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L4   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER:         2002:813875  CAPLUS
DOCUMENT NUMBER:          137:329436
TITLE:                    Prodrugs via acylation with cinnamate
INVENTOR(S):              Gilbert, Carl W.; McGowan, Eleanor B.; Black, Kirby
                          S.; Harper, Gregory T. P.
PATENT ASSIGNEE(S):       Cryolife, Inc., USA
SOURCE:                   PCT Int. Appl., 60 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
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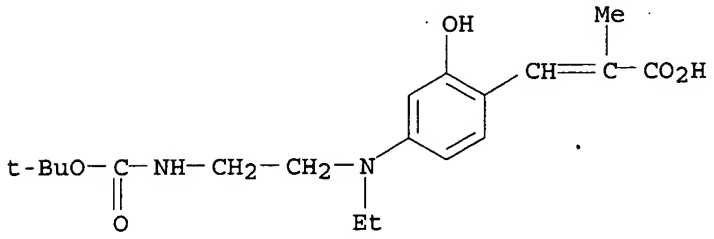
     WO 2002083067      A2   20021024       WO 2002-US11330  20020412
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     US 2002187992      A1   20021212       US 2002-66306    20020131
PRIORITY APPLN. INFO.:                     US 2001-284304P  P  20010417
                                           US 2001-315782P  P  20010828
                                           US 2002-66306    A  20020131
AB   A prodrug compn. contg. a cinnamate moiety and a biol. active mol. moiety
     which can be released by hydrolysis or activated by light is disclosed.
     The cinnamate moiety can have substituents of various electronically
     donating or electronically withdrawing groups to modify the cinnamate
     moiety's elec. properties as well as photo reactivities for the purpose of
     achieving a proper hydrolysis rate of the acyl bond between the biol.
     active mol. moiety and the cinnamic acid backbone.  The biol. active mol.
     can be any biol. active agent or diagnostic, for example, a
     chemotherapeutic such as a paclitaxel, camptothecin, doxorubicin,
     amethopterin, etoposide, or fluconazole.  The prodrug compn. can be
     modified to add a carrier moiety on the prodrug compn. for targeting or to
     facilitate uptake of the drug.  The prodrug compns. can be activated with
     an energy source to release the drug at the desired site.  Representative
     energy sources can be in the form of elec. force, ultrasound, light or
     radiation of a radioactive material which can be administered either
```

externally or internally.

IT **473440-37-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of prodrugs via acylation with cinnamate for drug release by hydrolysis or activation by energy source)

RN 473440-37-8 CAPLUS

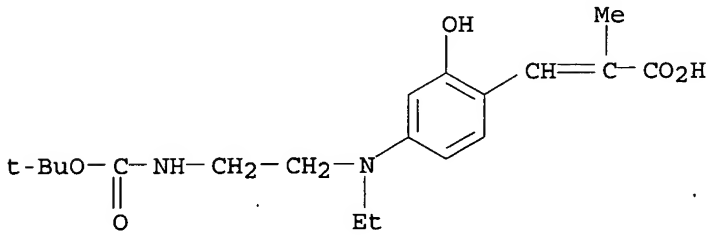
CN 2-Propenoic acid, 3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl- (9CI) (CA INDEX NAME)



IT **473440-37-8DP**, conjugates with polyethylene glycol and cytokine
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of prodrugs via acylation with cinnamate for drug release by hydrolysis or activation by energy source)

RN 473440-37-8 CAPLUS

CN 2-Propenoic acid, 3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl- (9CI) (CA INDEX NAME)



L4 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:813875 CAPLUS
DOCUMENT NUMBER: 137:329436
TITLE: Prodrugs via acylation with cinnamate
INVENTOR(S): Gilbert, Carl W.; McGowan, Eleanor B.; Black, Kirby S.; Harper, Gregory T. P.
PATENT ASSIGNEE(S): Cryolife, Inc., USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

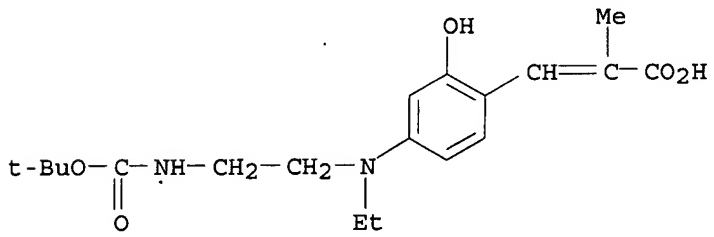
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002083067	A2	20021024	WO 2002-US11330	20020412
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002187992	A1	20021212	US 2002-66306	20020131

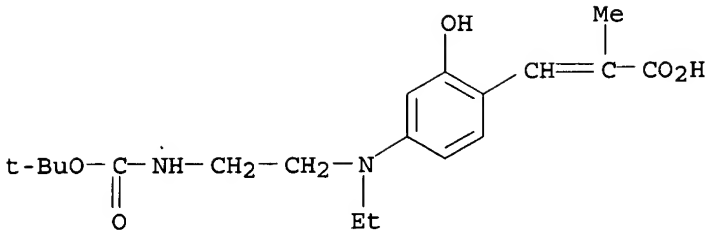
PRIORITY APPLN. INFO.:
US 2001-284304P P 20010417
US 2001-315782P P 20010828
US 2002-66306 A 20020131

AB A prodrug compn. contg. a cinnamate moiety and a biol. active mol. moiety which can be released by hydrolysis or activated by light is disclosed. The cinnamate moiety can have substituents of various electronically donating or electronically withdrawing groups to modify the cinnamate moiety's elec. properties as well as photo reactivities for the purpose of achieving a proper hydrolysis rate of the acyl bond between the biol. active mol. moiety and the cinnamic acid backbone. The biol. active mol. can be any biol. active agent or diagnostic, for example, a chemotherapeutic such as a paclitaxel, camptothecin, doxorubicin, amethopterin, etoposide, or fluconazole. The prodrug compn. can be modified to add a carrier moiety on the prodrug compn. for targeting or to facilitate uptake of the drug. The prodrug compns. can be activated with an energy source to release the drug at the desired site. Representative energy sources can be in the form of elec. force, ultrasound, light or radiation of a radioactive material which can be administered either externally or internally.

IT **473440-37-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of prodrugs via acylation with cinnamate for drug release by hydrolysis or activation by energy source)

RN 473440-37-8 CAPLUS
CN 2-Propenoic acid, 3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl- (9CI) (CA INDEX NAME)





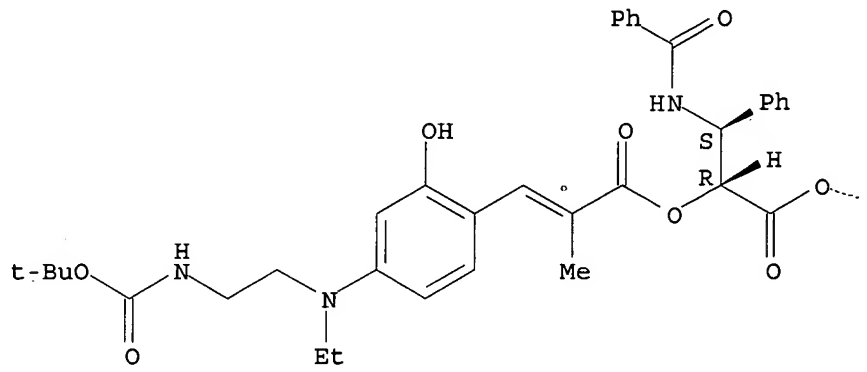
IT **473440-38-9P 473440-39-0P 473440-43-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of prodrugs via acylation with cinnamate for drug release by hydrolysis or activation by energy source)

RN 473440-38-9 CAPLUS

CN Benzenepropanoic acid, .beta.-(benzoylamino)-.alpha.-[[3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl-1-oxo-2-propenyl]oxy]-, (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, (.alpha.R,.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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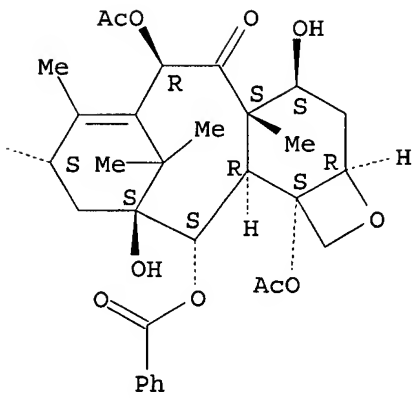
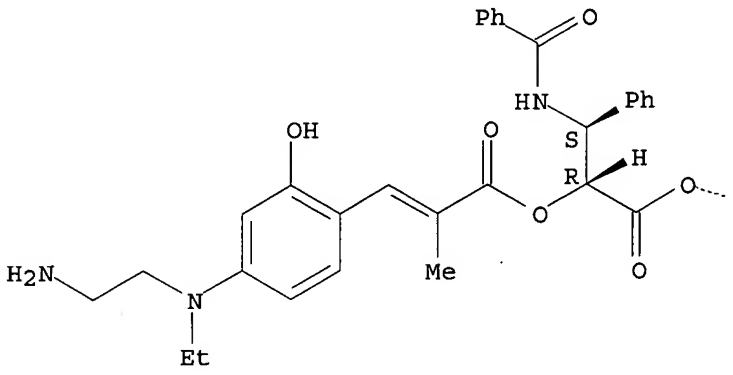


RN 473440-39-0 CAPLUS
CN Benzenepropanoic acid, .alpha.-[[3-[4-[(2-aminoethyl)ethylamino]-2-hydroxyphenyl]-2-methyl-1-oxo-2-propenyl]oxy]-.beta.-(benzoylamino)-, (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, (.alpha.R,.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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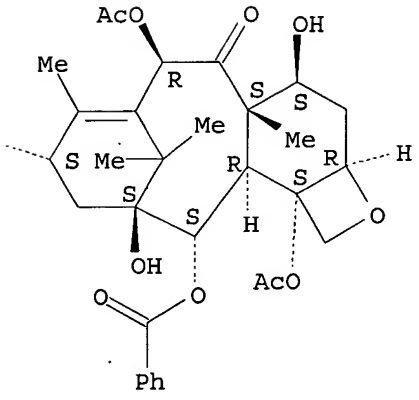
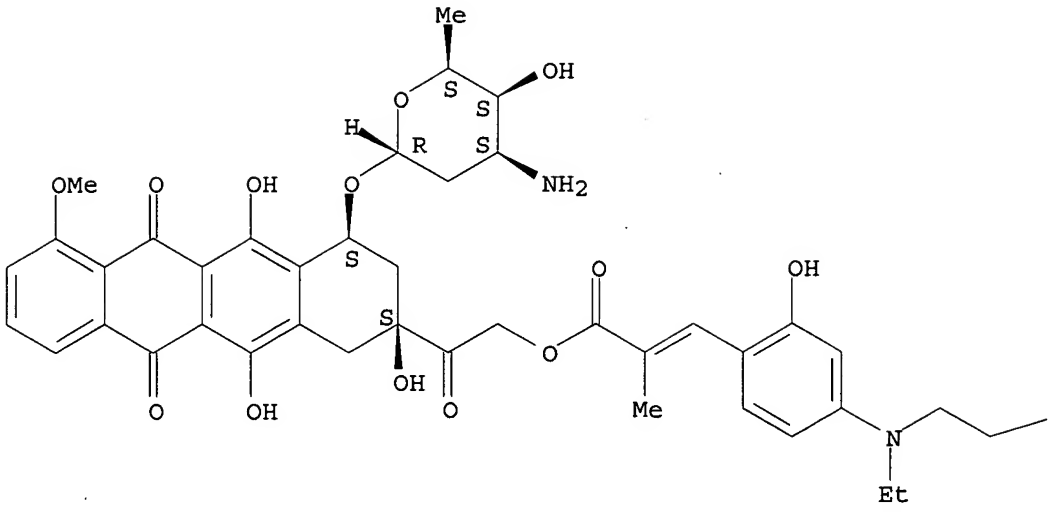


RN 473440-43-6 CAPLUS
CN 2-Propenoic acid, 3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl-, 2-[(2S,4S)-4-[(3-amino-2,3,6-trideoxy-.alpha.-L-lyxo-hexopyranosyl)oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]-2-oxoethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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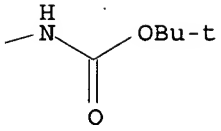
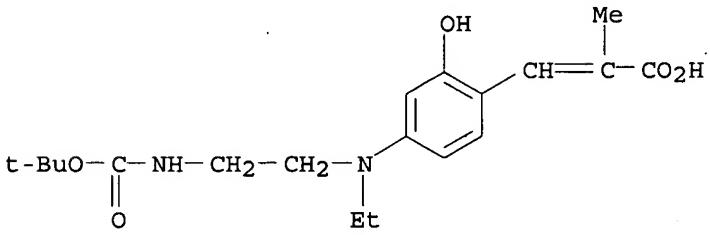
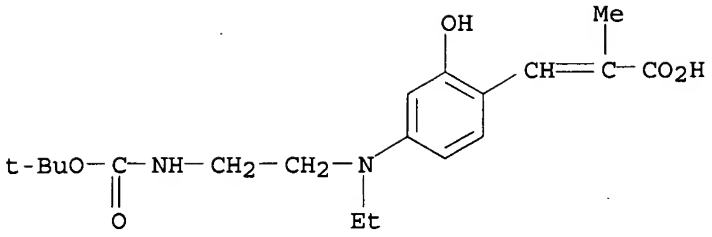


IT **473440-37-8DP**, conjugates with polyethylene glycol and cytokine
473440-41-4P 473440-44-7P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of prodrugs via acylation with cinnamate for drug release by hydrolysis or activation by energy source)

RN 473440-37-8 CAPLUS

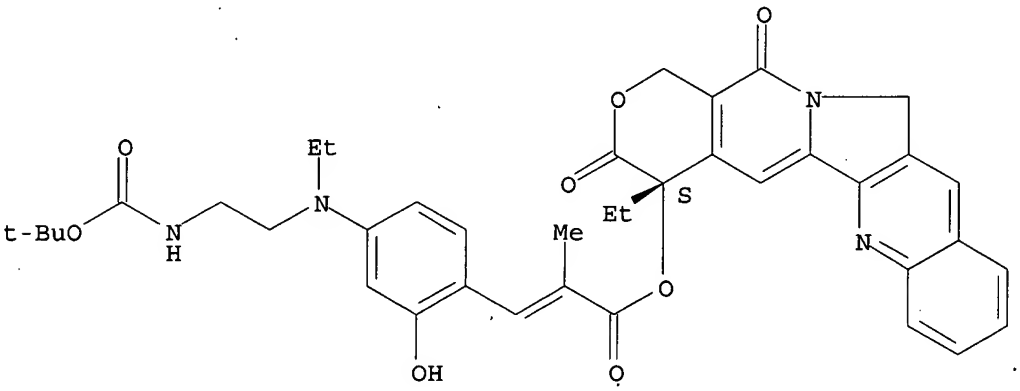
CN 2-Propenoic acid, 3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl- (9CI) (CA INDEX NAME)





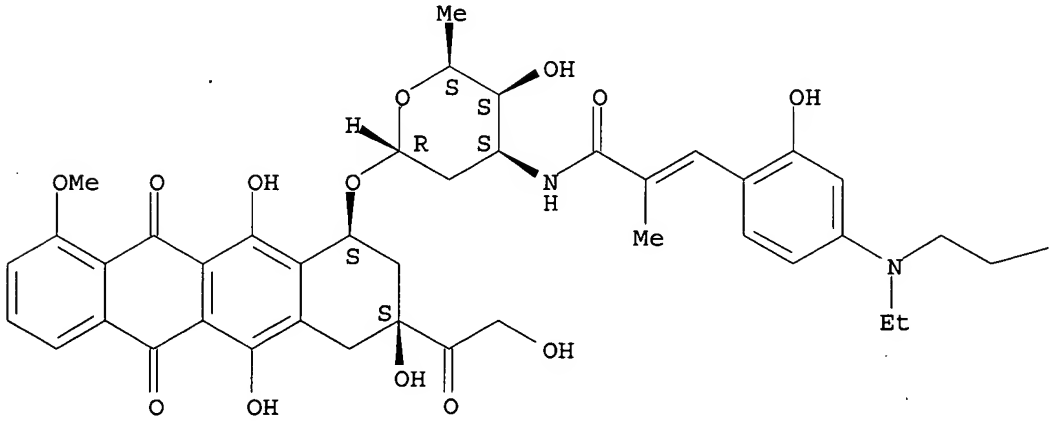
RN 473440-41-4 CAPLUS
CN 2-Propenoic acid, 3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl-, (4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl ester (9CI) (CA INDEX NAME)

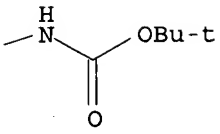
Absolute stereochemistry.
Double bond geometry unknown.



RN 473440-44-7 CAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl-1-oxo-2-propenyl]amino]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



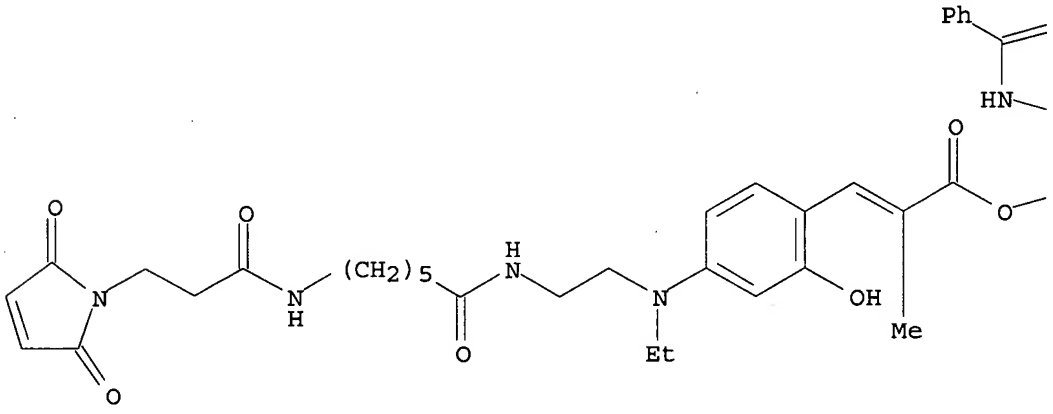


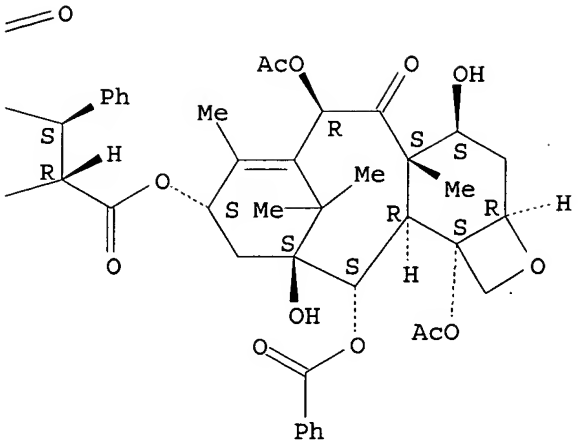
IT **473440-33-4 473440-34-5D**, conjugates with monoclonal antibodies **473440-35-6 473440-35-6D**, conjugates with monoclonal antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of prodrugs via acylation with cinnamate for drug release by hydrolysis or activation by energy source)

RN 473440-33-4 CAPLUS

CN Benzenepropanoic acid, .beta.-(benzoylamino)-.alpha.-[[3-[4-[[2-[[6-[[3-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-1-oxopropyl]amino]-1-oxohexyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl-1-oxo-2-propenyl]oxy]-, (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, (.alpha.R,.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.





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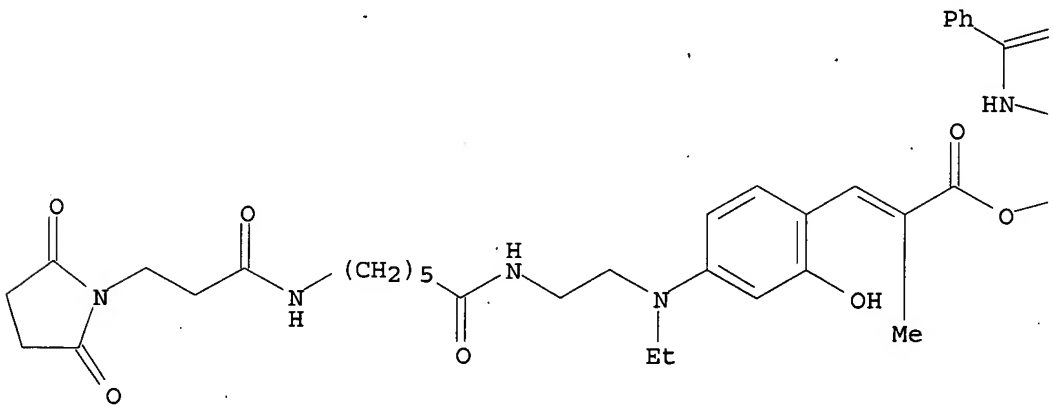
Absolute stereochemistry.
Double bond geometry unknown.



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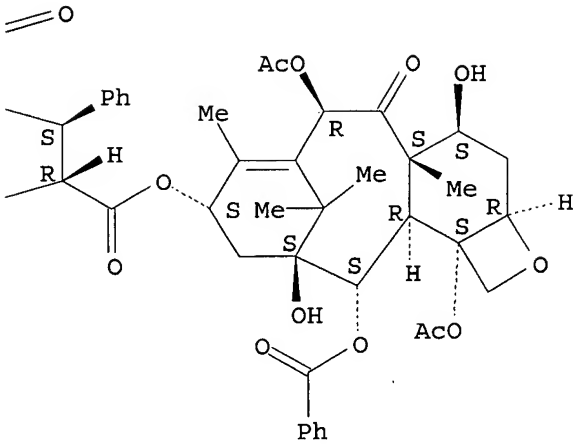

RN 473440-35-6 CAPLUS

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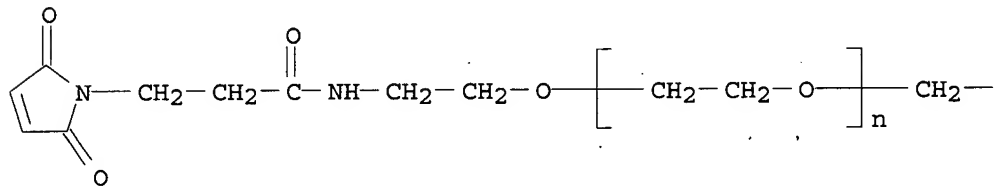
PAGE 1-A



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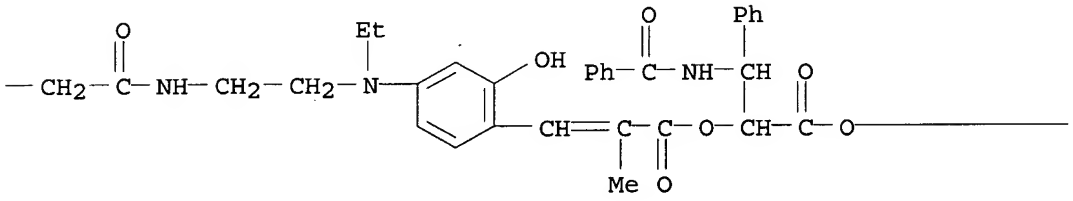

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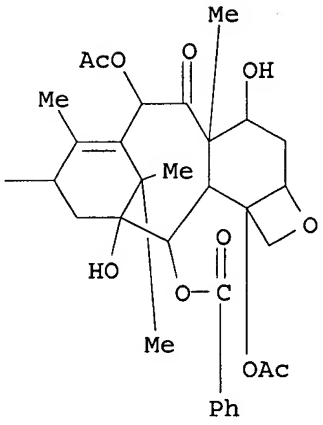

RN 473440-35-6 CAPLUS

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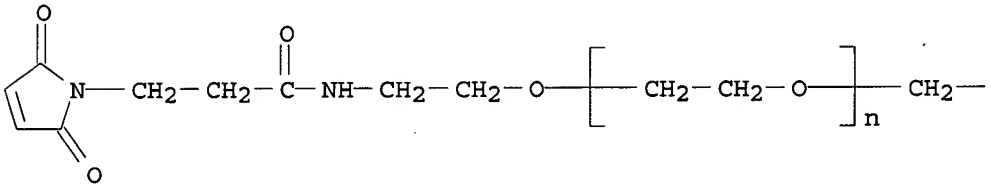
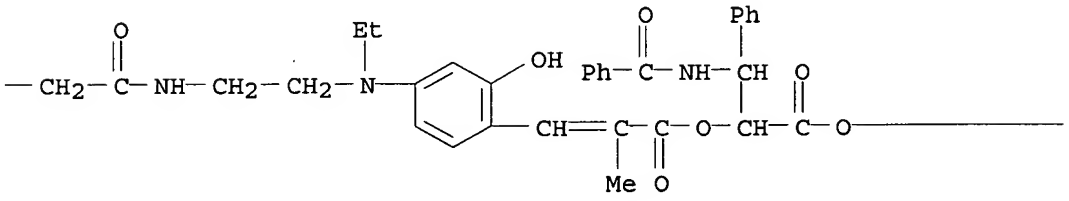
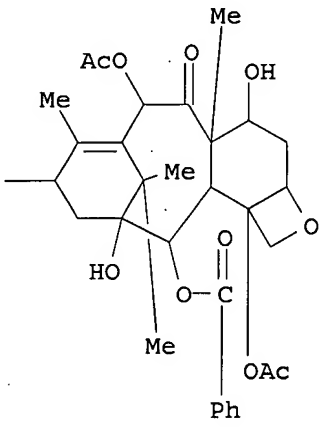


PAGE 1-B





L4 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:192042 CAPLUS
DOCUMENT NUMBER: 126:185882
TITLE: Substituted cinnamic acid guanidides, process for their preparation, their use as cardiovascular medicament or diagnostic agent, as well as medicament containing them
INVENTOR(S): Schwark, Jan-Robert; Brendel, Joachim; Kleemann, Heinz-Werner; Lang, Hans-Jochen; Weichert, Andreas; Albus, Udo; Scholz, Wolfgang
PATENT ASSIGNEE(S): Hoechst A.-G., Germany
SOURCE: Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 755919	A2	19970129	EP 1996-111665	19960719
EP 755919	A3	19970409		
EP 755919	B1	19991117		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
DE 19527305	A1	19970130	DE 1995-19527305	19950726
PL 183439	B1	20020628	PL 1996-314279	19960516
AT 186720	E	19991215	AT 1996-111665	19960719
ES 2140765	T3	20000301	ES 1996-111665	19960719
CN 1145899	A	19970326	CN 1996-110200	19960723
CN 1062554	B	20010228		
AU 9660668	A1	19970130	AU 1996-60668	19960724
AU 704461	B2	19990422		
US 5883133	A	19990316	US 1996-686999	19960724
IL 118925	A1	20010808	IL 1996-118925	19960724
SK 282018	B6	20011008	SK 1996-965	19960724
CZ 289327	B6	20020116	CZ 1996-2184	19960724
CA 2182062	AA	19970127	CA 1996-2182062	19960725
NO 9603108	A	19970127	NO 1996-3108	19960725
JP 09052823	A2	19970225	JP 1996-196283	19960725
HR 960356	B1	20010228	HR 1996-960356	19960725
BR 9603179	A	20020409	BR 1996-3179	19960725
RU 2190601	C2	20021010	RU 1996-115333	19960725

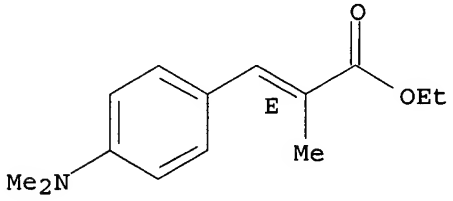
PRIORITY APPLN. INFO.: DE 1995-19527305 A 19950726
OTHER SOURCE(S): MARPAT 126:185882
AB Substituted cinnamic acid guanidides, such as E-3-(4-

Me2NC6H4)CH:CMeCON:N(NH2)2, were prepd. by the reaction of lithiated tri-Et 2-phosphonopropionate in hexane with 4-Me2NC6H4CHO, the resulting ester sapond., followed by reaction with cinnamic acid guanidide. These substituted cinnamic acid guanidides were tested as inhibitors for Na+/H+ exchange by rabbit erythrocytes, indicating their use as cardiovascular **drugs** or diagnostic agents.

IT **187541-48-6P 187541-49-7P 187541-57-7P 187541-58-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(for prepn. of substituted cinnamic acid guanidides)

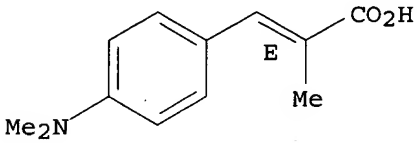
RN 187541-48-6 CAPLUS
CN 2-Propenoic acid, 3-[4-(dimethylamino)phenyl]-2-methyl-, ethyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



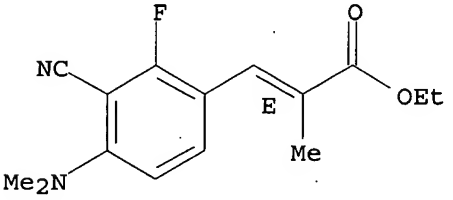
RN 187541-49-7 CAPLUS
CN 2-Propenoic acid, 3-[4-(dimethylamino)phenyl]-2-methyl-, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



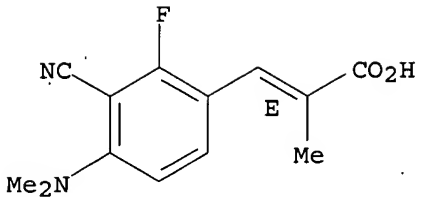
RN 187541-57-7 CAPLUS
CN 2-Propenoic acid, 3-[3-cyano-4-(dimethylamino)-2-fluorophenyl]-2-methyl-, ethyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



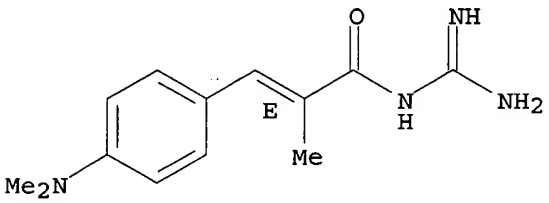
RN 187541-58-8 CAPLUS
CN 2-Propenoic acid, 3-[3-cyano-4-(dimethylamino)-2-fluorophenyl]-2-methyl-, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **187541-36-2P 187541-40-8P**
RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and use as cardiovascular **drugs** or diagnostic agents)
RN 187541-36-2 CAPLUS
CN 2-Propenamide, N-(aminoiminomethyl)-3-[4-(dimethylamino)phenyl]-2-methyl-, dihydrochloride, (E)- (9CI) (CA INDEX NAME)

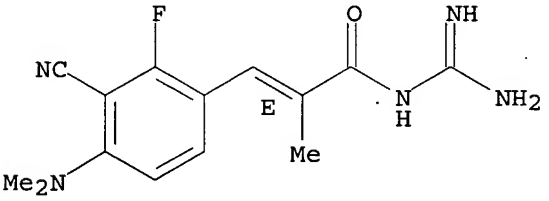
Double bond geometry as shown.



●2 HCl

RN 187541-40-8 CAPLUS
CN 2-Propenamide, N-(aminoiminomethyl)-3-[3-cyano-4-(dimethylamino)-2-fluorophenyl]-2-methyl-, dihydrochloride, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



●2 HCl

L4 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:169505 CAPLUS
DOCUMENT NUMBER: 124:249662
TITLE: Different Kinetic Pathways of the Binding of Two Biphenyl Analogs of Colchicine to Tubulin
AUTHOR(S): Dumortier, Chantal; Gorbunoff, Marina J.; Andreu, Jose M.; Engelborghs, Yves
CORPORATE SOURCE: Laboratory of Chemical and Biological Dynamics, Katholieke Universiteit Leuven, Louvain, B-3001, Belg.
SOURCE: Biochemistry (1996), 35(14), 4387-95
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
LANGUAGE: English

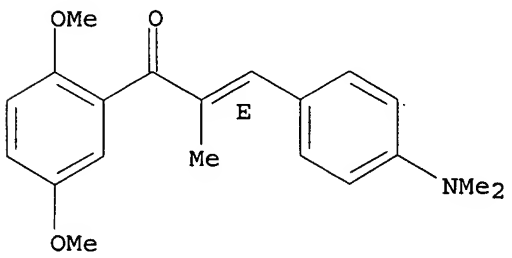
AB The kinetics of the interaction of tubulin with two biphenyl analogs of colchicine were measured by fluorescence stopped flow. The ligands were 2,3,4-trimethoxy-4'-carbomethoxy-1,1'-biphenyl (TCB) and 2,3,4-trimethoxy-4'-acetyl-1,1'-biphenyl (TKB). The binding of both analogs is accompanied by a fluorescence increase with monophasic kinetics, which indicates that these **drugs**, unlike colchicine, do not discriminate between the isoforms of tubulin. The obsd. pseudo-first-order rate const. increases in a nonlinear way with the drug concn., indicating that the binding of the biphenyl analogs to tubulin occurs, like colchicine, in two steps: a fast reversible equil. followed by an isomerization of the initial complex. Kinetic anal. shows that TCB and TKB exhibit differences in their K1 values. At 25.degree., these are 114,000 M-1 for TCB and 8300 M-1 for TKB. Both mols. show a much higher affinity than colchicine for the initial binding site. Also at 25.degree., the k2 value is 0.66 s-1 for TCB and 3.0 s-1 for TKB. From the temp. dependence, a reaction enthalpy change for the initial binding (.DELTA.H.degree.1) of 44 kJ.cntdot.mol-1(TCB) and -40 kJ.cntdot.mol-1 (TKB) and an activation energy for the second forward step of 64 kJ.cntdot.mol-1 (TCB) and 101 kJ.cntdot.mol-1 (TKB) were calcd. The dissocn. kinetics were studied by displacement expts., in which podophyllotoxin was used as a displacing ligand. The rate const. for the second step in the off direction (k-2) is 0.25 s-1 for TCB and 0.093 s-1 for TKB at 25.degree.. The activation energies for the backward isomerization of the complexes were found to be 86 kJ.cntdot.mol-1 (TCB) and 79 kJ.cntdot.mol-1 (TKB). Combination of these results with the kinetic parameters for assocn. gives a full characterization of the enthalpy pathway for the binding of TCB and TKB. The pathway of TCB binding is shown to differ considerably from that of TKB binding. Since their structural difference is located in ring C', this result points to their use of the ring C' in the first binding step. The competitiveness of the binding of TCB and TKB with those of podophyllotoxin, MTC, and MDL 27048 indicates that the two biphenyls interact as well with the trimethoxyphenyl-specific subsite.

IT **124711-23-5**, MDL 27048
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(for binding competition expts.; different kinetic pathways of binding of two biphenyl analogs of colchicine to tubulin)

RN 124711-23-5 CAPLUS

CN 2-Propen-1-one, 1-(2,5-dimethoxyphenyl)-3-[4-(dimethylamino)phenyl]-2-methyl-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

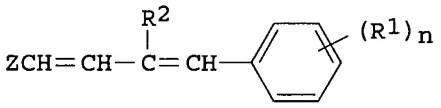


L4 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1990:98395 CAPLUS
DOCUMENT NUMBER: 112:98395
TITLE: Butadienylheterocycles as **drugs** and their preparation
INVENTOR(S): Konishi, Mitsuhiro; Tanaka, Hiroshi; Osuge, Kunio;

	Haga, Keiichiro
PATENT ASSIGNEE(S):	Yoshitomi Pharmaceutical Industries, Ltd., Japan
SOURCE:	Jpn. Kokai Tokkyo Koho, 15 pp.
	CODEN: JKXXAF
DOCUMENT TYPE:	Patent
LANGUAGE:	Japanese
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 01175966	A2	19890712	JP 1987-335487	19871229
WO 9100275	A1	19910110	WO 1989-JP637	19890627
W: US				
RW: AT, BE, CH, DE, FR, GB, IT, NL, SE				
PRIORITY APPLN. INFO.:			JP 1987-335487	19871229

GI



I

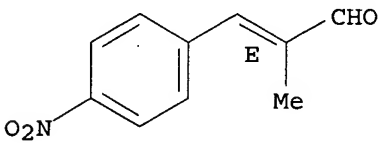
AB The title compds. (I; R1 = H, halo, NO2, cyano, etc.; when at least one of R1 is lower alkanoylamino, alkanoyloxyalkanoylamino, etc., R2 is H, lower alkyl; in other cases R2 = lower alkyl; n = 1-5; Z = pyridyl, pyrimidinyl, etc.), useful as **drugs** (no data), were prepd. Wittig reaction of .alpha.-methyl-4-fluorocinnamaldehyde with the Wittig reagent prepd. from 4-chloromethylpyridine and Ph3P gave cis- and trans-4-[4-(4-fluorophenyl)-3-methyl-1,3-butadienyl]pyridines.

IT **58550-34-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in prepn. of drug)

RN 58550-34-8 CAPLUS

CN 2-Propenal, 2-methyl-3-(4-nitrophenyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



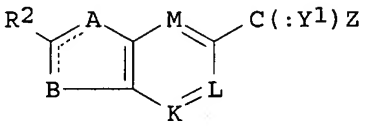
d l5 1-2 ibib abs hitstr

L5 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:97397 CAPLUS
DOCUMENT NUMBER: 138:153436
TITLE: Preparation of indole-6-carboxamides and related compounds as hepatitis C viral polymerase inhibitors
INVENTOR(S): Beaulieu, Pierre Louis; Fazal, Gulrez; Goulet, Sylvie; Kukolj, George; Poirier, Martin; Tsantrizos, Youla S.; Jolicoeur, Eric; Gillard, James; Poupart, Marc-Andre; Rancourt, Jean
PATENT ASSIGNEE(S): Boehringer Ingelheim (Canada) Ltd., Can.
SOURCE: PCT Int. Appl., 336 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

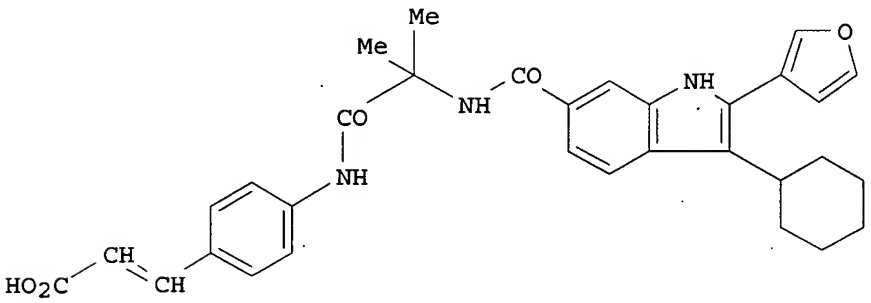
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003010141	A2	20030206	WO 2002-CA1128	20020718
WO 2003010141	A3	20030530		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-307674P P 20010725
US 2001-338061P P 20011207
OTHER SOURCE(S): MARPAT 138:153436
GI



I



II

AB An isomer, enantiomer, diastereoisomer or tautomer of I (variables defined below; e.g. (E)-3-[4-[2-[[1-(3-cyclohexyl-2-furan-3-yl-1H-indol-6-yl)methanoyl]amino]-2-methylpropanoylamino]phenyl]acrylic acid (shown as

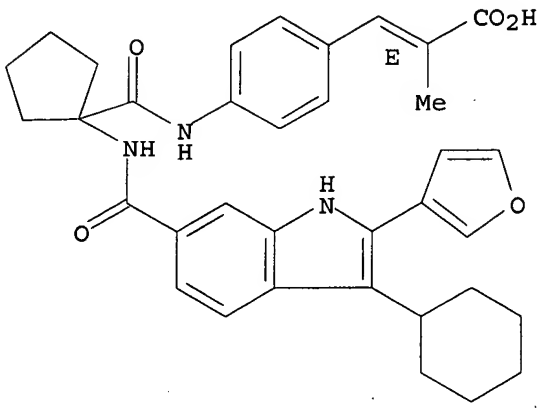
II)), a salt or a deriv. thereof, as inhibitors of HCV NS5B polymerase are claimed. For I: A is O, S, NR1, or CR1; solid line/dotted line combination = single or double bond; R2 = H, halogen, R21, OR21, SR21, COOR21, SO2N(R22)2, N(R22)2, CON(R22)2, NR22C(O)R22 or NR22C(O)NR22; B is NR3 or CR3, with the proviso that one of A or B is either CR1 or CR3; K is N or CR4; L is N or CR4; M is N or CR4; Y1 is O or S; Z is N(R6a)R6 or OR6, wherein R6a is H or alkyl or NR61R62; and R6 is H, alkyl, cycloalkyl, alkenyl, Het, alkyl-aryl, alkyl-Heterocycle or CR7R8C(:Y2)NR9Q; Y2 is O or S; R9 is H, (C1-6)alkyl, (C3-7)cycloalkyl or (C1-6)alkyl-(C3-7)cycloalkyl, aryl, Het, (C1-6)alkyl-aryl or (C1-6)alkyl-Het, all of which optionally are substituted with R90; or R9 is covalently bonded to either of R7 or R8 to form a 5- or 6-membered heterocycle; other variables are defined in the claims. About 350 I were tested for inhibitory activity against the hepatitis C virus RNA dependent polymerase (NS5B), e.g. IC50 < 500 nM for II. Forty-five example prepns. of I and intermediates are included. For example, 3-cyclohexyl-2-(furan-3-yl)-1H-indol-6-carboxylic acid (0.16 mmol), (E)-3-[4-(2-Amino-2-methylpropanoylamino)phenyl]acrylic acid Et ester (0.019 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.32 mmol) were dissolved in DMSO (1 mL); iPr2EtN (0.8 mmol) was added; the mixt. was stirred for 1 h at room temp. then treated with 2.5 N NaOH (0.3 mL) for 1 h at 50.degree. to affect hydrolysis of the cinnamate ester function; the mixt. was then acidified to pH 1 with trifluoroacetic acid and II was isolated by preparative reversed-phase HPLC (0.033 g). Preps. of the above reactants are also included.

IT **494854-86-3P**, N-(1-(((4-((E)-2-Carboxy-1-propenyl)phenyl)amino)carbonyl)cyclopentyl)-3-cyclohexyl-2-(furan-3-yl)indole-6-carboxamide **494857-30-6P**, N-(1-(((4-((E)-2-Carboxy-1-propenyl)phenyl)amino)carbonyl)cyclobutyl)-1-methyl-3-cyclopentyl-2-(pyridin-2-yl)indole-6-carboxamide **494857-33-9P**, N-(1-(((4-((E)-2-Carboxy-1-propenyl)phenyl)amino)carbonyl)cyclobutyl)-1-methyl-3-cyclopentyl-2-(3-aminophenyl)indole-6-carboxamide **494857-38-4P**, N-(1-(((4-((E)-2-Carboxy-1-propenyl)phenyl)amino)carbonyl)cyclobutyl)-1-methyl-3-cyclopentyl-2-(4-aminophenyl)indole-6-carboxamide **494857-43-1P**, N-(1-(((4-((E)-2-Carboxy-1-propenyl)phenyl)amino)carbonyl)cyclobutyl)-1-methyl-3-cyclopentyl-2-(6-methylpyridin-2-yl)indole-6-carboxamide **494857-47-5P**, N-(1-(((4-((E)-2-Carboxy-1-propenyl)phenyl)amino)carbonyl)cyclobutyl)-1-methyl-3-cyclopentyl-2-(6-aminopyridin-2-yl)indole-6-carboxamide **494857-52-2P**, N-(1-(((4-((E)-2-Carboxy-1-propenyl)phenyl)amino)carbonyl)cyclobutyl)-1-methyl-3-cyclopentyl-2-(5-methylpyridin-2-yl)indole-6-carboxamide **494857-56-6P**, N-(1-(((4-((E)-2-Carboxy-1-propenyl)phenyl)amino)carbonyl)cyclobutyl)-1-methyl-3-cyclopentyl-2-(6-methylpyridin-3-yl)indole-6-carboxamide **494857-60-2P**, N-(1-(((4-((E)-2-Carboxy-1-propenyl)phenyl)amino)carbonyl)cyclobutyl)-1-methyl-3-cyclopentyl-2-(pyrazin-2-yl)indole-6-carboxamide **494857-66-8P**, N-(1-(((4-((E)-2-Carboxy-1-propenyl)phenyl)amino)carbonyl)cyclobutyl)-1-methyl-3-cyclopentyl-2-(4-ethylpyridin-2-yl)indole-6-carboxamide **494857-73-7P**, N-(1-(((4-((E)-2-Carboxy-1-propenyl)phenyl)amino)carbonyl)cyclobutyl)-1-methyl-3-cyclopentyl-2-(thiazol-2-yl)indole-6-carboxamide **494857-78-2P**, N-(1-(((4-((E)-2-Carboxy-1-propenyl)phenyl)amino)carbonyl)cyclobutyl)-1-methyl-3-cyclopentyl-2-(thien-3-yl)indole-6-carboxamide
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; prepn. of indole-6-carboxamides and related compds. as hepatitis C viral polymerase inhibitors)

RN 494854-86-3 CAPLUS

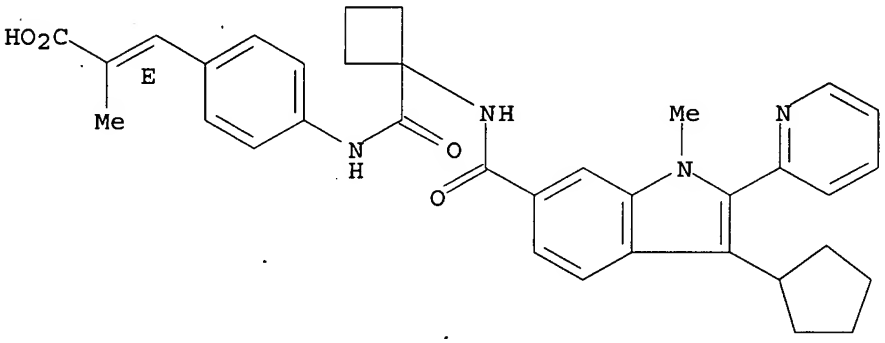
CN 2-Propenoic acid, 3-[4-[[[1-[[[3-cyclohexyl-2-(3-furanyl)-1H-indol-6-yl]carbonyl]amino]cyclopentyl]carbonyl]amino]phenyl]-2-methyl-, (2E)-(9CI) (CA INDEX NAME)

Double bond geometry as shown.



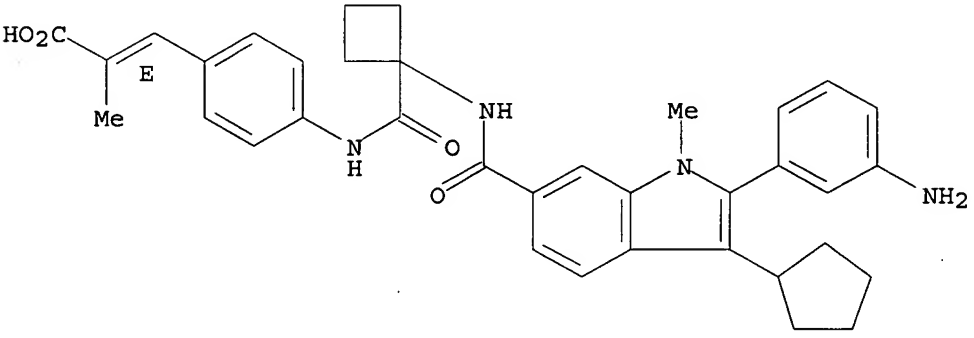
RN 494857-30-6 CAPLUS
CN 2-Propenoic acid, 3-[4-[[[1-[[[3-cyclopentyl-1-methyl-2-(2-pyridinyl)-1H-indol-6-yl]carbonyl]amino]cyclobutyl]carbonyl]amino]phenyl]-2-methyl-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 494857-33-9 CAPLUS
CN 2-Propenoic acid, 3-[4-[[[1-[[[2-(3-aminophenyl)-3-cyclopentyl-1-methyl-1H-indol-6-yl]carbonyl]amino]cyclobutyl]carbonyl]amino]phenyl]-2-methyl-, (2E)- (9CI) (CA INDEX NAME)

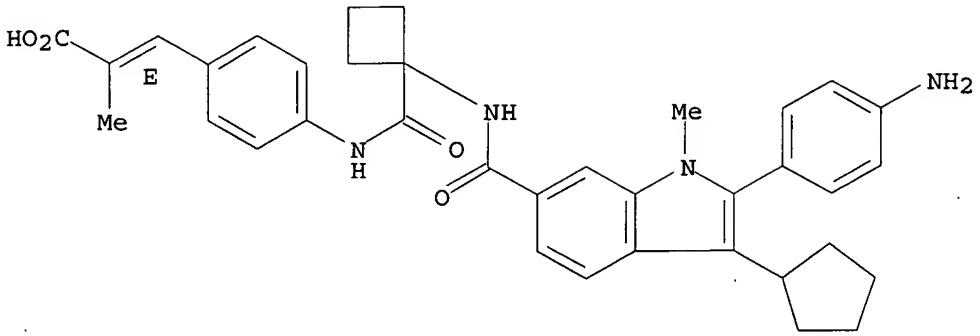
Double bond geometry as shown.



RN 494857-38-4 CAPLUS
CN 2-Propenoic acid, 3-[4-[[[1-[[[2-(4-aminophenyl)-3-cyclopentyl-1-methyl-1H-indol-6-yl]carbonyl]amino]cyclobutyl]carbonyl]amino]phenyl]-2-methyl-,

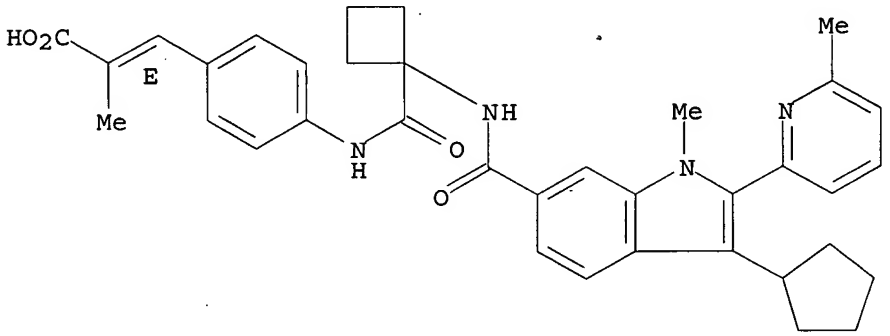
(2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



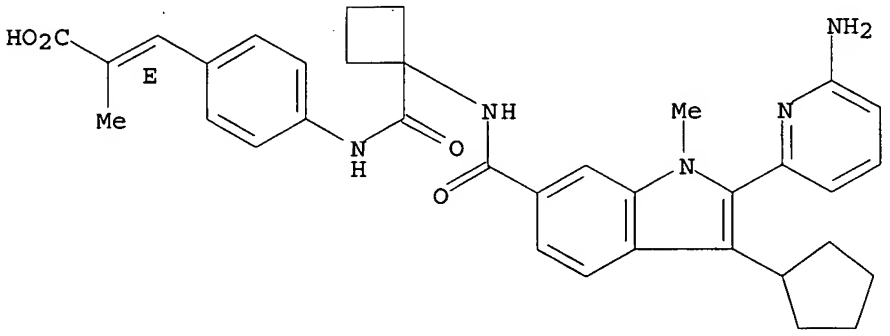
RN 494857-43-1 CAPLUS
CN 2-Propenoic acid, 3-[4-[[[1-[[[3-cyclopentyl-1-methyl-2-(6-methyl-2-pyridinyl)-1H-indol-6-yl]carbonyl]amino]cyclobutyl]carbonyl]amino]phenyl]-2-methyl-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



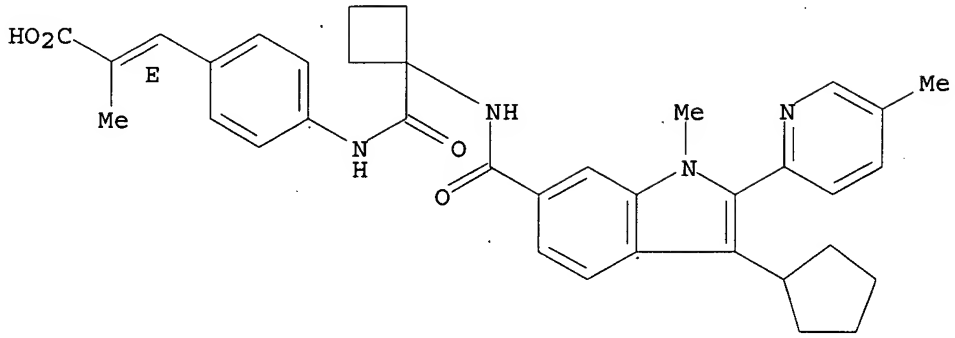
RN 494857-47-5 CAPLUS
CN 2-Propenoic acid, 3-[4-[[[1-[[[2-(6-amino-2-pyridinyl)-3-cyclopentyl-1-methyl-1H-indol-6-yl]carbonyl]amino]cyclobutyl]carbonyl]amino]phenyl]-2-methyl-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



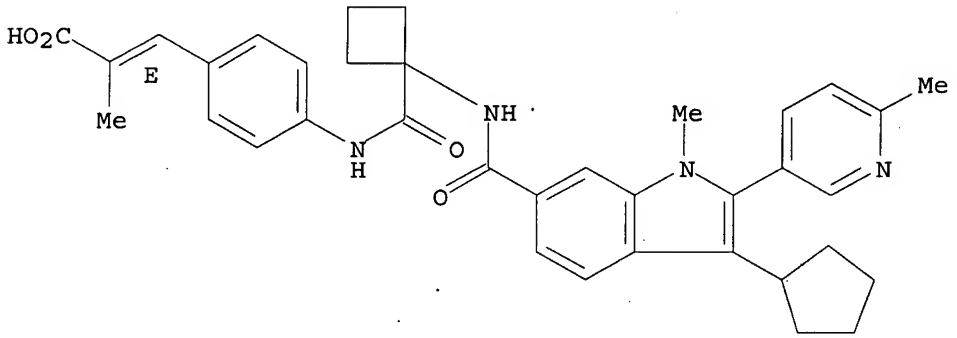
RN 494857-52-2 CAPLUS
CN 2-Propenoic acid, 3-[4-[[[1-[[[3-cyclopentyl-1-methyl-2-(5-methyl-2-pyridinyl)-1H-indol-6-yl]carbonyl]amino]cyclobutyl]carbonyl]amino]phenyl]-2-methyl-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



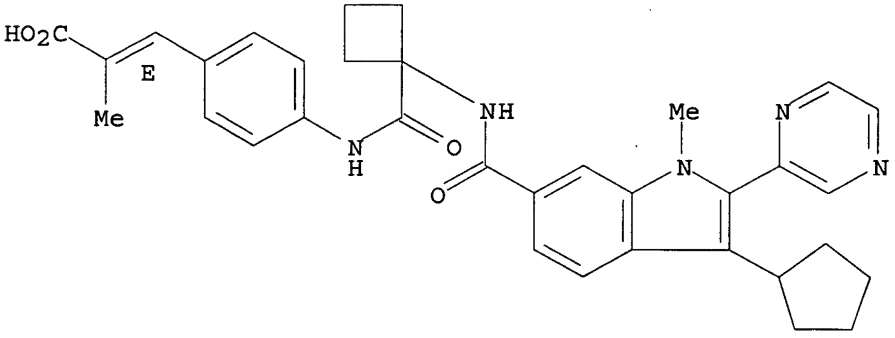
RN 494857-56-6 CAPLUS
CN 2-Propenoic acid, 3-[4-[[[1-[[[3-cyclopentyl-1-methyl-2-(6-methyl-3-pyridinyl)-1H-indol-6-yl]carbonyl]amino]cyclobutyl]carbonyl]amino]phenyl]-2-methyl-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



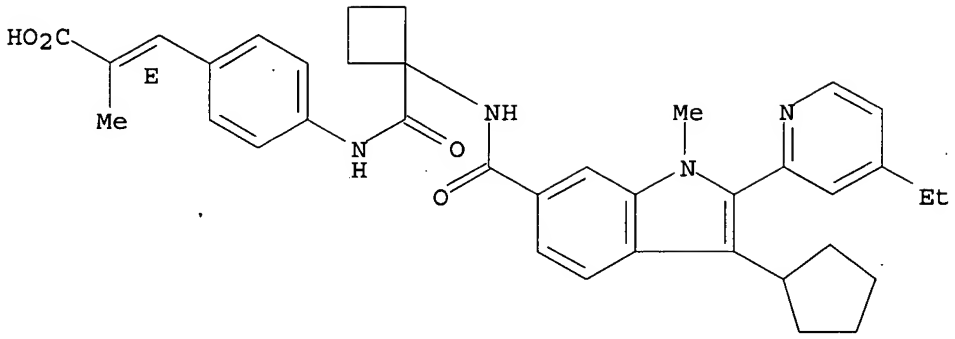
RN 494857-60-2 CAPLUS
CN 2-Propenoic acid, 3-[4-[[[1-[[(3-cyclopentyl-1-methyl-2-pyrazinyl-1H-indol-6-yl)carbonyl]amino]cyclobutyl]carbonyl]amino]phenyl]-2-methyl-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



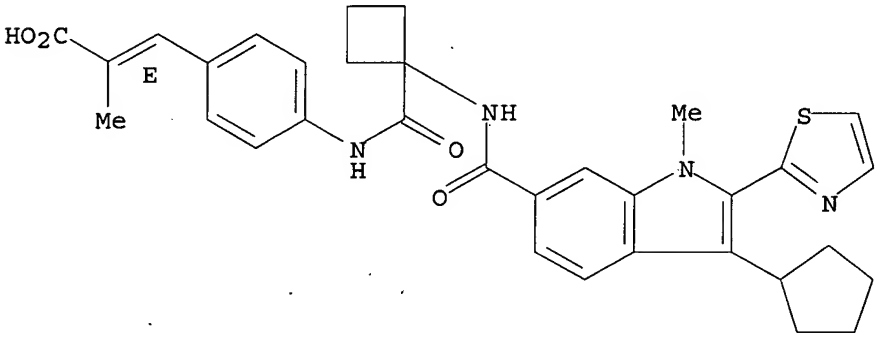
RN 494857-66-8 CAPLUS
CN 2-Propenoic acid, 3-[4-[[[1-[[[3-cyclopentyl-2-(4-ethyl-2-pyridinyl)-1-methyl-1H-indol-6-yl]carbonyl]amino]cyclobutyl]carbonyl]amino]phenyl]-2-methyl-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



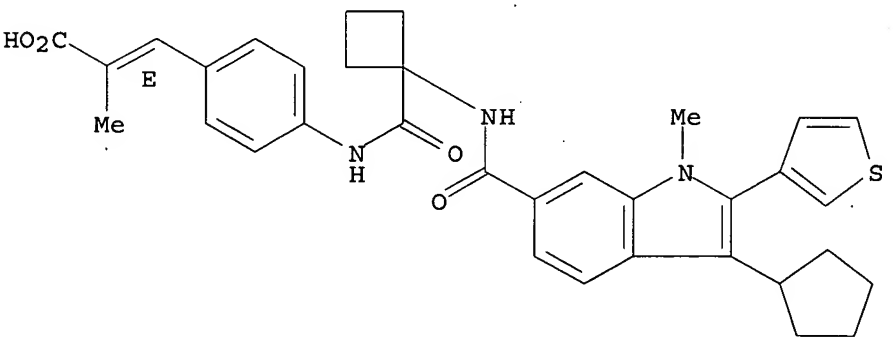
RN 494857-73-7 CAPLUS
CN 2-Propenoic acid, 3-[4-[[[1-[[[3-cyclopentyl-1-methyl-2-(2-thiazolyl)-1H-indol-6-yl]carbonyl]amino]cyclobutyl]carbonyl]amino]phenyl]-2-methyl-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



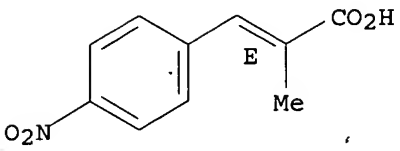
RN 494857-78-2 CAPLUS
CN 2-Propenoic acid, 3-[4-[[[1-[[[3-cyclopentyl-1-methyl-2-(3-thienyl)-1H-indol-6-yl]carbonyl]amino]cyclobutyl]carbonyl]amino]phenyl]-2-methyl-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



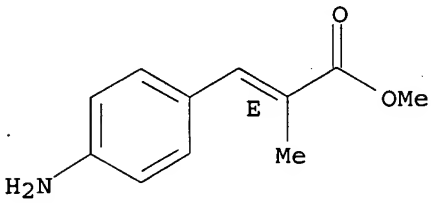
IT **13048-77-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of indole-6-carboxamides and related compds. as hepatitis C viral polymerase inhibitors)
RN 13048-77-6 CAPLUS
CN 2-Propenoic acid, 2-methyl-3-(4-nitrophenyl)-, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **494854-22-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of indole-6-carboxamides and related compds. as hepatitis C viral polymerase inhibitors)
RN 494854-22-7 CAPLUS
CN 2-Propenoic acid, 3-(4-aminophenyl)-2-methyl-, methyl ester, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L5 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:813875 CAPLUS
DOCUMENT NUMBER: 137:329436
TITLE: Prodrugs via acylation with cinnamate
INVENTOR(S): Gilbert, Carl W.; McGowan, Eleanor B.; Black, Kirby S.; Harper, Gregory T. P.
PATENT ASSIGNEE(S): Cryolife, Inc., USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002083067	A2	20021024	WO 2002-US11330	20020412
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002187992	A1	20021212	US 2002-66306	20020131

PRIORITY APPLN. INFO.:
US 2001-284304P P 20010417
US 2001-315782P P 20010828
US 2002-66306 A 20020131

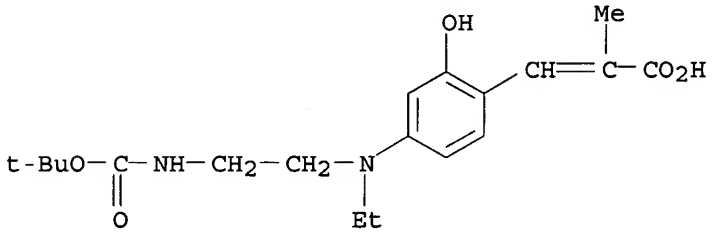
AB A prodrug compn. contg. a cinnamate moiety and a biol. active mol. moiety which can be released by hydrolysis or activated by light is disclosed. The cinnamate moiety can have substituents of various electronically

donating or electronically withdrawing groups to modify the cinnamate moiety's elec. properties as well as photo reactivities for the purpose of achieving a proper hydrolysis rate of the acyl bond between the biol. active mol. moiety and the cinnamic acid backbone. The biol. active mol. can be any biol. active agent or diagnostic, for example, a chemotherapeutic such as a paclitaxel, camptothecin, doxorubicin, amethopterin, etoposide, or fluconazole. The prodrug compn. can be modified to add a carrier moiety on the prodrug compn. for targeting or to facilitate uptake of the drug. The prodrug compns. can be activated with an energy source to release the drug at the desired site. Representative energy sources can be in the form of elec. force, ultrasound, light or radiation of a radioactive material which can be administered either externally or internally.

IT **473440-37-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of prodrugs via acylation with cinnamate for drug release by hydrolysis or activation by energy source)

RN 473440-37-8 CAPLUS

CN 2-Propenoic acid, 3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl- (9CI) (CA INDEX NAME)

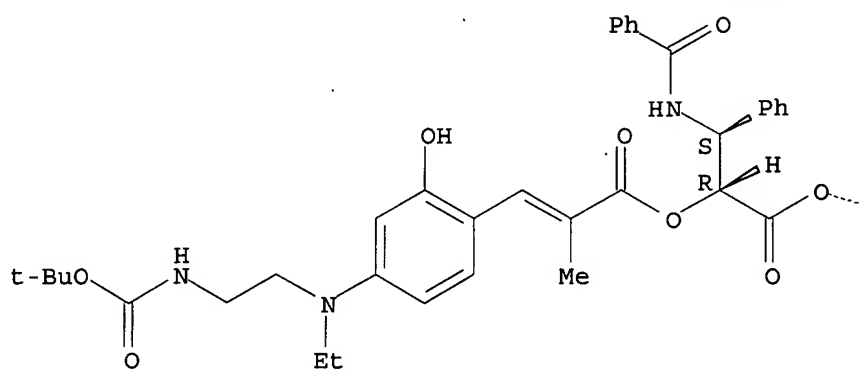


IT **473440-38-9P 473440-39-0P 473440-43-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of prodrugs via acylation with cinnamate for drug release by hydrolysis or activation by energy source)

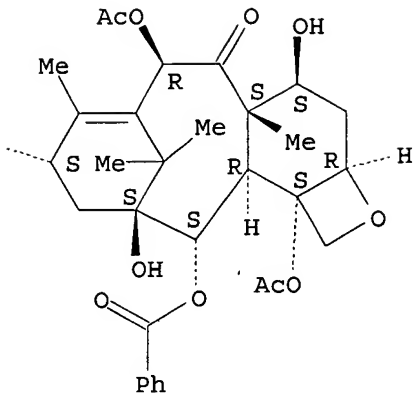
RN 473440-38-9 CAPLUS

CN Benzenepropanoic acid, .beta.-(benzoylamino)-.alpha.-[[3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl-1-oxo-2-propenyl]oxy]-, (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, (.alpha.R,.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



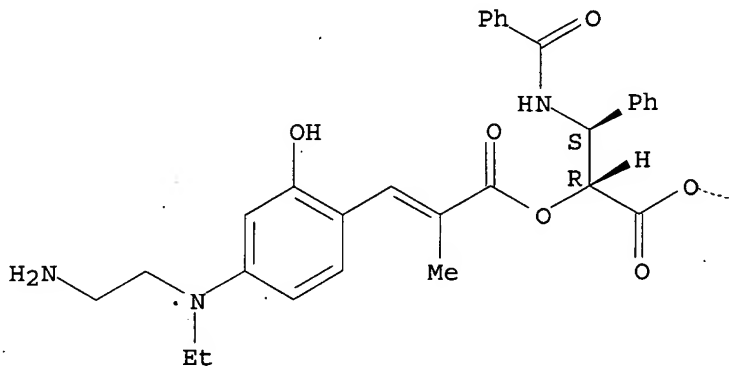
PAGE 1-B



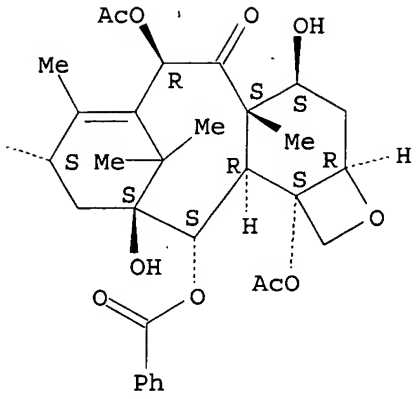
RN 473440-39-0 CAPLUS
CN Benzenepropanoic acid, .alpha.-[[3-[4-[(2-aminoethyl)ethylamino]-2-hydroxyphenyl]-2-methyl-1-oxo-2-propenyl]oxy]-.beta.-(benzoylamino)-, (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, (.alpha.R,.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 1-B

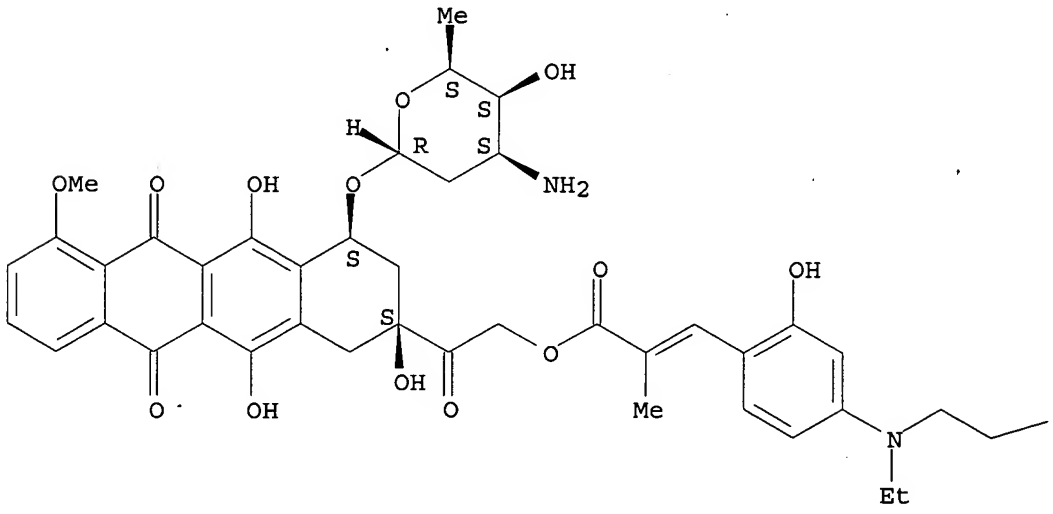


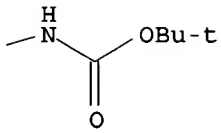
RN 473440-43-6 CAPLUS

CN 2-Propenoic acid, 3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl-, 2-[(2S,4S)-4-[(3-amino-2,3,6-trideoxy-.alpha.-L-lyxo-hexopyranosyl)oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]-2-oxoethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A

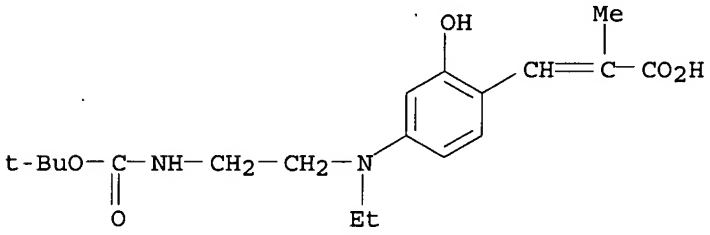




IT **473440-37-8DP**, conjugates with polyethylene glycol and cytokine
473440-41-4P 473440-44-7P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of prodrugs via acylation with cinnamate for drug release by hydrolysis or activation by energy source)

RN 473440-37-8 CAPLUS

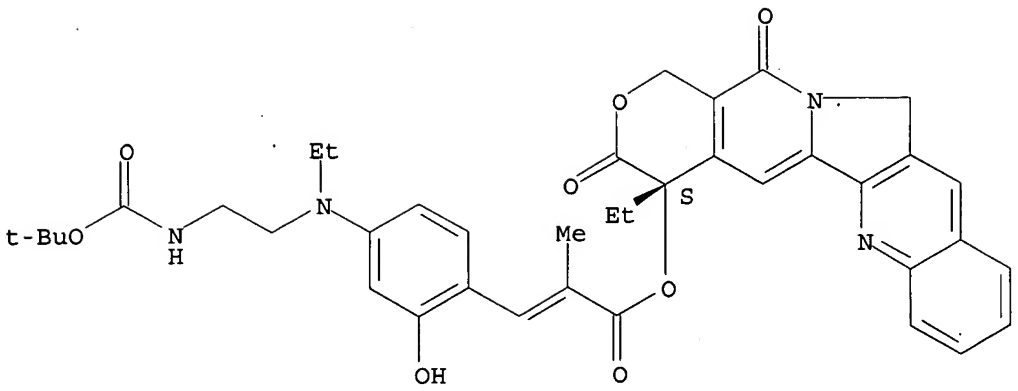
CN 2-Propenoic acid, 3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl- (9CI) (CA INDEX NAME)



RN 473440-41-4 CAPLUS

CN 2-Propenoic acid, 3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl-, (4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl ester (9CI) (CA INDEX NAME)

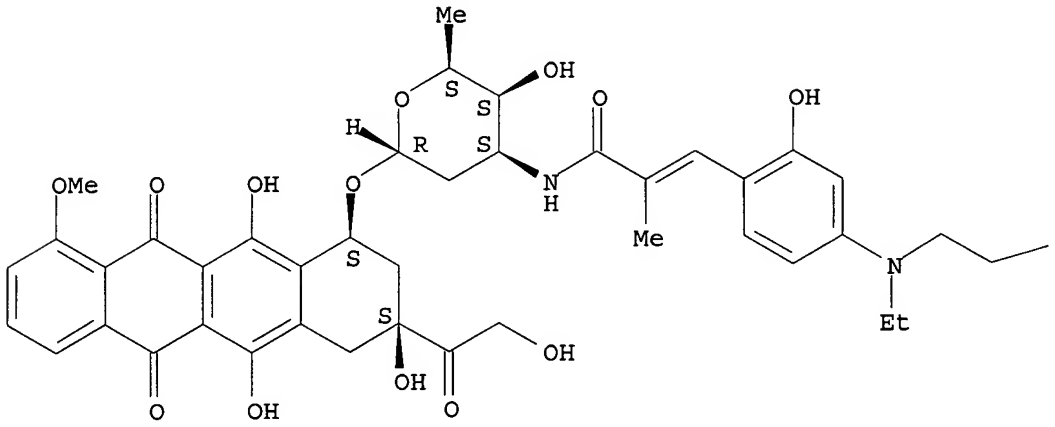
Absolute stereochemistry.
Double bond geometry unknown.



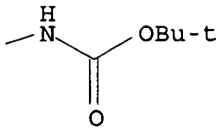
RN 473440-44-7 CAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[3-[4-[[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl-1-oxo-2-propenyl]amino]-.alpha.-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 1-B



IT **473440-33-4 473440-34-5D**, conjugates with monoclonal

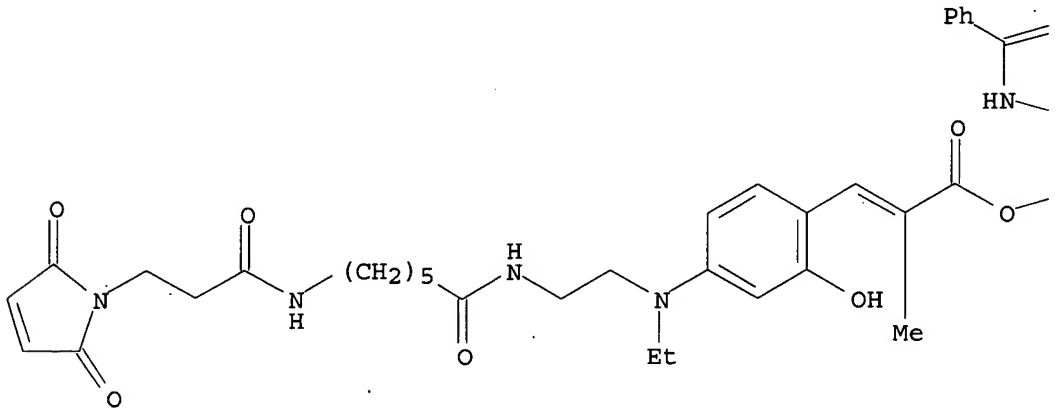
antibodies **473440-35-6 473440-35-6D**, conjugates with monoclonal antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of prodrugs via acylation with cinnamate for drug release by hydrolysis or activation by energy source)

RN 473440-33-4 CAPLUS

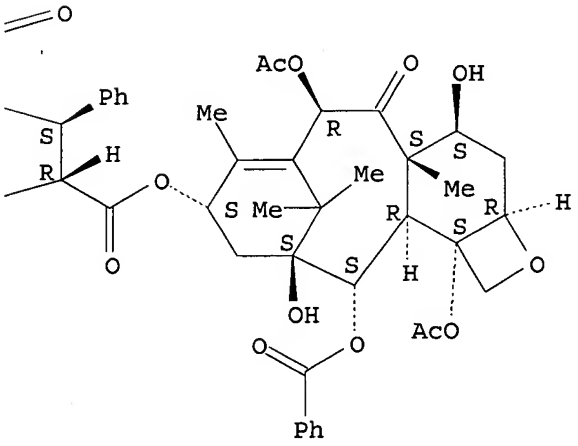
CN Benzenepropanoic acid, .beta.-(benzoylamino)-.alpha.-[[3-[4-[[2-[[6-[[3-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-1-oxopropyl]amino]-1-oxohexyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl-1-oxo-2-propenyl]oxy]-, (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, (.alpha.R,.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 1-B



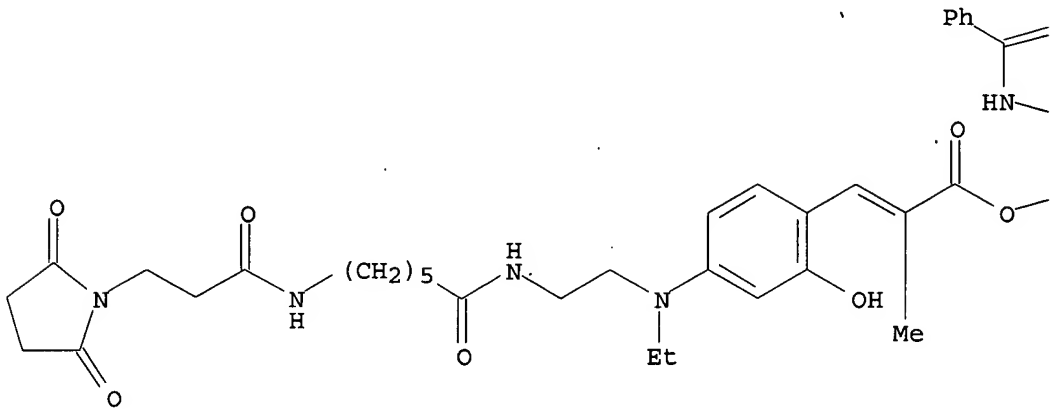
RN 473440-34-5 CAPLUS

CN Benzenepropanoic acid, .beta.-(benzoylamino)-.alpha.-[[3-[4-[[2-[[6-[[3-(2,5-dioxo-1-pyrrolidinyl)-1-oxopropyl]amino]-1-oxohexyl]amino]ethyl]ethylamino]-2-hydroxyphenyl]-2-methyl-1-oxo-2-propenyl]oxy]-, (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-

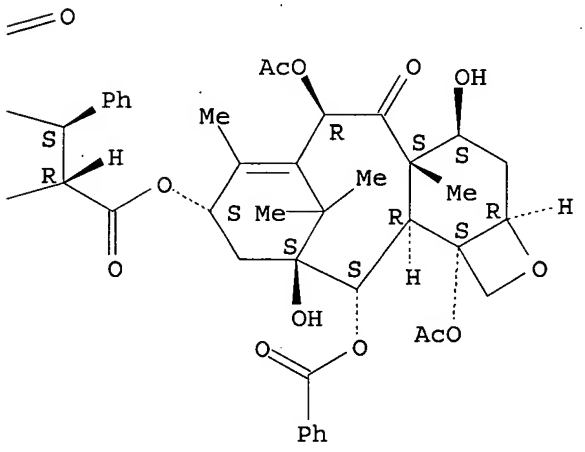
dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, (.alpha.R,.beta.S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A

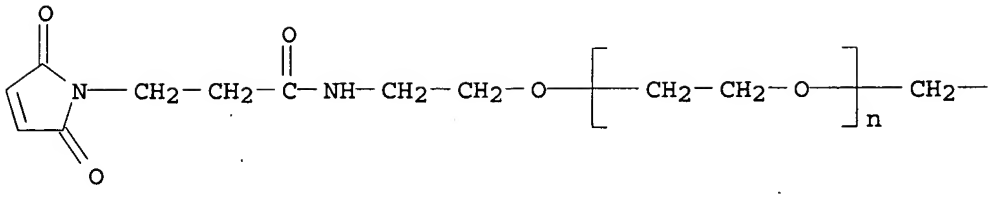


PAGE 1-B

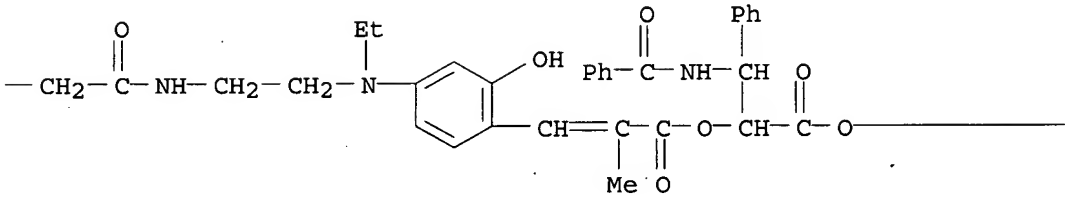


RN 473440-35-6 CAPLUS
CN Poly(oxy-1,2-ethanediyl), .alpha.-[3-[[2-[[4-[3-[(1R,2S)-1-[[[(2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl]oxy]carbonyl]-2-(benzoylamino)-2-phenylethoxy]-2-methyl-1-oxo-1-propenyl]-3-hydroxyphenyl]ethylamino]ethyl]amino]-3-oxopropyl]-.omega.-[2-[[3-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-1-oxopropyl]amino]ethoxy]- (9CI) (CA INDEX NAME)

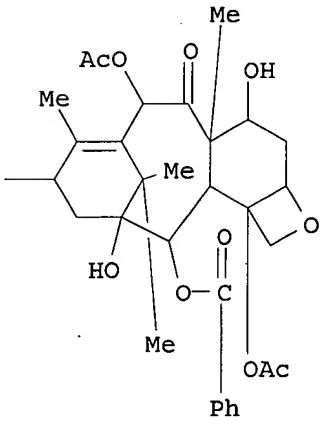
PAGE 1-A



PAGE 1-B



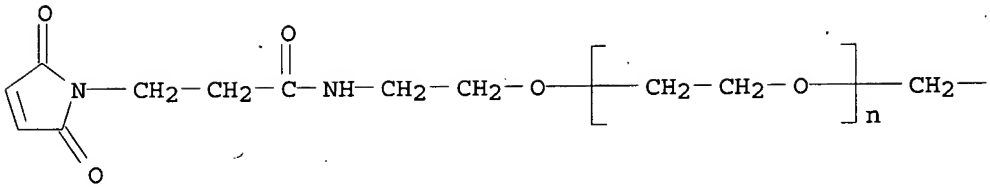
PAGE 1-C



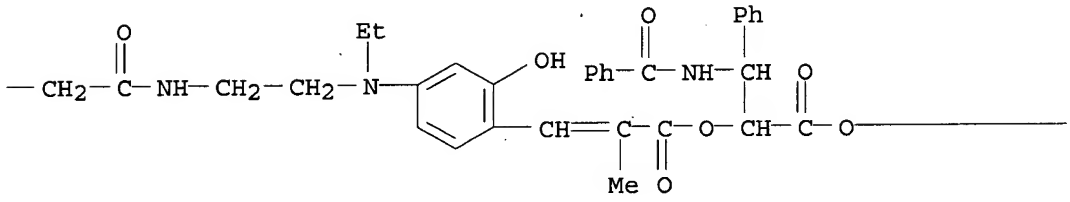
RN 473440-35-6 CAPLUS

CN Poly(oxy-1,2-ethanediyl), .alpha.-[3-[[2-[[4-[3-[(1R,2S)-1-[[[(2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl]oxy]carbonyl]-2-(benzoylamino)-2-phenylethoxy]-2-methyl-1-oxo-1-propenyl]-3-hydroxyphenyl]ethylamino]ethyl]amino]-3-oxopropyl]-.omega.-[2-[[3-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-1-oxopropyl]amino]ethoxy]- (9CI) (CA INDEX NAME)

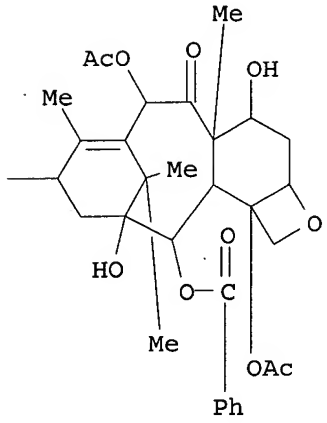
PAGE 1-A



PAGE 1-B

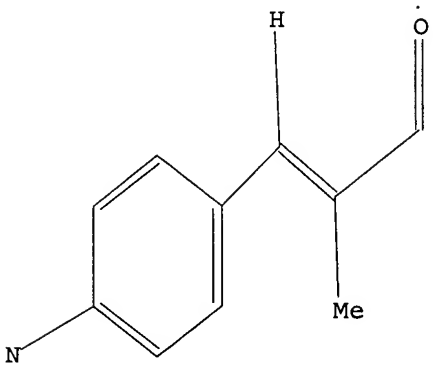


PAGE 1-C



L5 2 S L3 AND DRUG DELIVERY

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

d l8 1-4 ibib abs hitstr

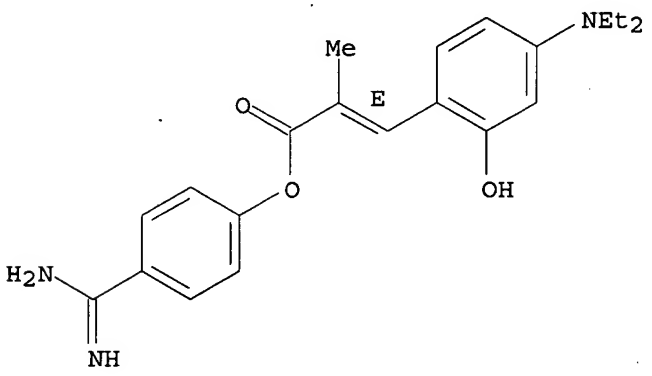
L8 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:528156 CAPLUS
DOCUMENT NUMBER: 127:218530
TITLE: In vivo photoactivation of caged-thrombin
AUTHOR(S): Arroyo, Jorge G.; Jones, Paul B.; Porter, Ned A.; Hatchell, Diane L.
CORPORATE SOURCE: Department Ophthalmology, Duke University, Durham, NC, 27710, USA
SOURCE: Thrombosis and Haemostasis (1997), 78(2), 791-793
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: Schattauer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aberrant ocular neovascularization is a major cause of blindness in the world. Abnormal blood vessels in the eye may produce corneal opacification, corneal transplant rejection, neovascular glaucoma, vitreous hemorrhage, traction retinal detachment, and subretinal scars from choroidal neovascular membranes. Light-induced clotting of blood within these abnormal vessels could provide a novel method for the ablation of deleterious neovascularization. Thrombin is a Ser proteinase that participates in the final stages of the coagulation cascade. P-amidinophenyl-(E)-4-diethylamino-2-hydroxy-.alpha.-methylcinnamate hydrochloridean inhibitor of thrombin, p-amidinophenyl-(E)-4-diethylamino-2-hydroxy-.alpha.-methylcinnamate hydrochloride, MeCINN, covalently attaches to the active site Ser hydroxyl, inhibiting or caging, the enzyme. Photolysis of the caged-thrombin in vitro causes a trans-cis isomerization of MeCINN which leads to regeneration of active enzyme and **cleaving** of fibrinogen into fibrin. Using a rabbit model of corneal neovascularization, it was found that light at 366 nm safely and effectively photoactivates i.v. caged-thrombin and produces localized thrombosis in vivo. These results suggest that intra-vascular photoactivation of caged-thrombin could be used to occlude abnormal blood vessels in the human eye.

IT **189570-73-8**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(photoactivation of caged-thrombin in eye blood vessel)

RN 189570-73-8 CAPLUS
CN 2-Propenoic acid, 3-[4-(diethylamino)-2-hydroxyphenyl]-2-methyl-, 4-(aminoiminomethyl)phenyl ester, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L8 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1990:226654 CAPLUS

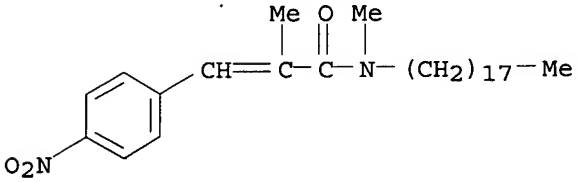
DOCUMENT NUMBER: 112:226654
TITLE: Silver halide photographic material containing fog inhibitor-releasing compound
INVENTOR(S): Furuya, Keizo; Nakamura, Takeki; Watanabe, Hiroyuki; Yoshioka, Yasuhiro
PATENT ASSIGNEE(S): Fuji Photo Film Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 77 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 01161237	A2	19890623	JP 1987-319989	19871217
JP 07117726	B4	19951218		
US 4994363	A	19910219	US 1988-286562	19881219

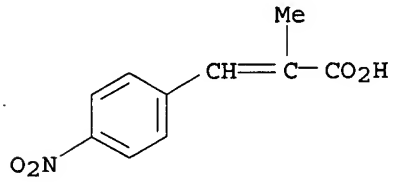
PRIORITY APPLN. INFO.: JP 1987-319989 19871217

AB The title photog. material contains EAGCR1:CR2(ETG)eCR3R4(Time)tPUG [EAG = arom. group receiving electron from reducing material; R1 = H, substituent; R2 = electron-accepting groups; position of R1 and R2 is cis or trans; R3, R4 = H, hydrocarbons; ETG = electron-transfer group; e = 0, 1; Time = PUG-releasing group via **cleavage** of C retaining R3 and R4; t = 0, 1; PUG = photog. useful group]. The PUG can be released right on the time.

IT **125576-63-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and use of, as fog inhibitor-releasing compd.)
RN 125576-63-8 CAPLUS
CN 2-Propenamide, N,2-dimethyl-3-(4-nitrophenyl)-N-octadecyl- (9CI) (CA INDEX NAME)



IT **949-98-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and use of, as photog. fog inhibitor releasing material)
RN 949-98-4 CAPLUS
CN 2-Propenoic acid, 2-methyl-3-(4-nitrophenyl)- (9CI) (CA INDEX NAME)



L8 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1973:453470 CAPLUS
DOCUMENT NUMBER: 79:53470
TITLE: Mechanism of the formation of phosphonium salts.

.alpha.-Alkyl-.beta.,.gamma.-dioxophosphonium salts and phosphoranes

AUTHOR(S): Shevchuk, M. I.; Khalaturnik, M. V.; Dombrovskii, A. V.

CORPORATE SOURCE: Chernovits. Gos. Univ., Chernovtsy, USSR

SOURCE: Zhurnal Obshchei Khimii (1973), 43(4), 758-63
CODEN: ZOKHA4; ISSN: 0044-460X

DOCUMENT TYPE: Journal

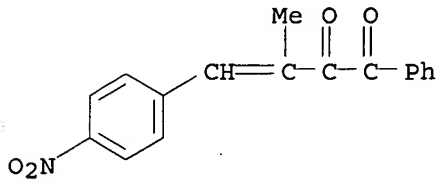
LANGUAGE: Russian

AB PPh3 and BrCH2COAr initially form labile enolic phosphonium salts at the CO group, which are converted to ion pairs and then irreversibly converted to the stable quaternary phosphonium salts Ph3P+CH2COAr Br-. ArCOCHBrR (R > C2) forms only the unstable enolic salts whih can isomerize to the ion pair or react with atm. H2O to form Ph3P(OH)OCAr:CHR which **cleaved** spontaneously to Ph3PO and the appropriate ketone. The formation of the enolic salt was confirmed by treating the initial ppt. from PPh3 and p-phenylphenacyl bromide with PhNH2 which gave Ph3P and PhNH2.HBr as well as PhNHCH2COC6H4Ph-p. PPh3 and p-RC6H4COCOCHBrR1 gave stable Ph3P+CHR1COCOAr Br- which dehydrobrominated with Na2CO3 in DMF to Ph3P:CR1COCOAr (R = H; p-Cl, p-Me; R1 = Me, Et, Pr). The enolic salt intermediates from bromo diketones with Ph3P could not be isolated. The stable onium salts were apparently formed by nucleophilic attack at the Br atom which is **cleaved** as Br+, after which the ion pair forms the onium salt. Treating PhNH2 with PPh3 gave on further addn. of BrCH2COCOAr Ph3P:NPh which can form only from an ion pair contg. electrophilic P. Thus PPh3 and BrCHRCOAr form onium salts by a SN2 reaction from nucleophilic attack at the carbonyl O atom; the analogous diketones also react by SN2 route by attack at the Br atom. Ph3P:CR1COCOAr react normally in the Wittig reaction, yielding substituted vinyl diketones. The unsatd. di- and triketones form 2,4-dinitrophenylhydrazones normally. BzCOCR:CHR1 (R = Me; R1 = Bz, p-O2NC6H4) were prepd.

IT **41843-15-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 41843-15-6 CAPLUS

CN 3-Butene-1,2-dione, 3-methyl-4-(4-nitrophenyl)-1-phenyl- (9CI) (CA INDEX NAME)



L8 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1959:111539 CAPLUS

DOCUMENT NUMBER: 53:111539

ORIGINAL REFERENCE NO.: 53:19948f-h

TITLE: Carbonyl reactions. VIII. The kinetics of the acid-catalyzed condensation of benzaldehyde and p-nitrobenzaldehyde with methyl ethyl ketone. Some observations on p-.sigma. correlations

AUTHOR(S): Noyce, Donald S.; Snyder, Lloyd R.

CORPORATE SOURCE: Univ. of California, Berkeley

SOURCE: Journal of the American Chemical Society (1959), 81, 620-4
CODEN: JACSAT; ISSN: 0002-7863

DOCUMENT TYPE: Journal

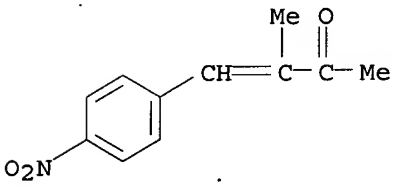
LANGUAGE: Unavailable

AB In the PhCHO-MeCOEt H2SO4-catalyzed system in HOAc, condensation yielding 4-phenyl-3-methyl-3-buten-2-one (I) occurred between the protonated salt of the aldehyde and the enol of MeCOEt. Concn. of I increased with time and concn. of PhCHO, reached a max. after 9400 sec., and further reaction was 1st-order elimination of the intermediate acetate. Condensation of p-nitrobenzaldehyde was similar but without evidence of **cleavage** and esterification of the intermediate .beta.-hydroxyketone. Rate of the **cleavage** reaction increased with electron-donating ring substituents. The esterification step was possibly solvolytic esterification of the alc. Elimination steps showed little dependence on structure. Utility of the .rho.-.sigma. correlation was discussed.

IT **26480-64-8**, 3-Buten-2-one, 3-methyl-4-(p-nitrophenyl)- (prepn. of)

RN 26480-64-8 CAPLUS

CN 3-Buten-2-one, 3-methyl-4-(4-nitrophenyl)- (9CI) (CA INDEX NAME)



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L2             37 S L1 SSS SAM
L3            683 S L1 SSS FULL

     FILE 'CAPLUS' ENTERED AT 14:05:53 ON 08 AUG 2003
L4              6 S L3 AND DRUGS
L5              2 S L3 AND DRUG DELIVERY
L6              2 S L3 AND DOXORUBICIN
L7              0 S L3 AND CLEAVABLE
L8              4 S L3 AND CLEAV?
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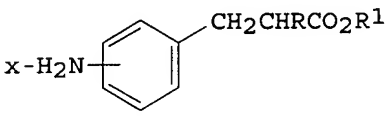
L10 ANSWER 10 OF 27 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1980:180835 CAPLUS
DOCUMENT NUMBER: 92:180835
TITLE: Aryl m- or p-aminophenylpropionates
INVENTOR(S): Fujii, Setsuro; Kawamura, Hiroyuki; Taira, Seizo; Matsui, Ryoji; Sakurai, Yojiro; Okutome, Toshiyuki
PATENT ASSIGNEE(S): Torii and Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

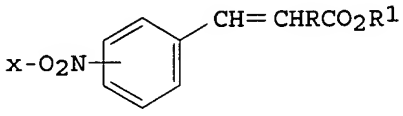
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 54135741	A2	19791022	JP 1978-44078	19780414
JP 61041340	B4	19860913		
US 4182897	A	19800108	US 1978-917232	19780620
NL 7806755	A	19781228	NL 1978-6755	19780622
NL 177018	B	19850218		
NL 177018	C	19850716		
CH 642056	A	19840330	CH 1978-6814	19780622
GB 2000133	A	19790104	GB 1978-27739	19780623
GB 2000133	B2	19820217		
FR 2395250	A1	19790119	FR 1978-18825	19780623
FR 2395250	B1	19810612		
DE 2827657	A1	19790201	DE 1978-2827657	19780623
DE 2827657	C2	19830519		

PRIORITY APPLN. INFO.:
JP 1977-75063 19770624
JP 1977-75064 19770624
JP 1978-44078 19780414
JP 1978-44079 19780414

GI



I

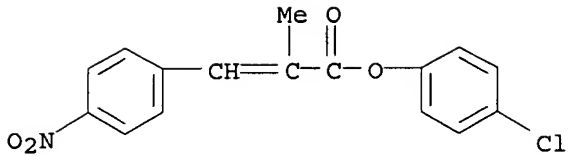


II

AB Sixteen aryl **esters** I (x = m, p; R = H, Me, Et; R1 = p-tolyl, p-chlorophenyl, 1-naphthyl, C6H4CH2CO2H-p, etc.), inhibiting thrombin or trypsin activity with Me N-tosylargininate as the substrate, were prepd. via II. Thus, 19.3 g p-nitrocinnamic acid treated with 22 g PCl5 in EtOAc and the chloride stirred with 10.8 g p-cresol and 12 g Et3N in EtOAc at room temp. gave 95% II (x = p, R = H, R1 = p-tolyl), which was hydrogenated over 10% Pd-C in EtOH to give 87.7% corresponding I.HCl.

IT **69693-37-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and hydrogenation of)

RN 69693-37-4 CAPLUS
CN 2-Propenoic acid, 2-methyl-3-(4-nitrophenyl)-, 4-chlorophenyl ester (9CI) (CA INDEX NAME)

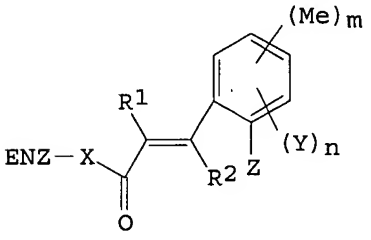

Me
O
CH
C
C
O
O2N
Cl

L11 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1991:651031 CAPLUS
DOCUMENT NUMBER: 115:251031
TITLE: Light activated acyl-**enzymes**
INVENTOR(S): Porter, Ned A.; Bruhnke, John D.
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9103549	A1	19910321	WO 1990-US4872	19900827
W: AU, CA, JP, KR				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
US 5114851	A	19920519	US 1989-400507	19890829
CA 2065008	AA	19910301	CA 1990-2065008	19900827
CA 2065008	C	19950801		
AU 9063319	A1	19910408	AU 1990-63319	19900827
AU 636269	B2	19930422		
EP 489836	A1	19920617	EP 1990-913585	19900827
EP 489836	B1	19941221		
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
JP 05500004	T2	19930114	JP 1990-512544	19900827
JP 2839371	B2	19981216		
ES 2067044	T3	19950316	ES 1990-913585	19900827
US 5218137	A	19930608	US 1992-857390	19920325

PRIORITY APPLN. INFO.: US 1989-400507 19890829
WO 1990-US4872 19900827

OTHER SOURCE(S): MARPAT 115:251031
GI

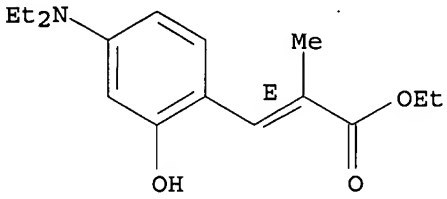


I

AB The title acyl-enzyme (I; ENZ = enzyme selected from serine proteinases when X = O or OH in the catalytic center of ENZ and cysteine proteinase when X = S or SH in the catalytic center of ENZ; Y = NR3R4, OR5, SR5; Z = OH, SH, NH2, NHR6; R6 = C1-4 alkyl; m = 0-3; n, 1, 2; R1, R2, R3 = H, C1-4 alkyl, C3-4 unconjugated alkenyl or alkynyl; R2 = H, C1-4 alkyl; R4, R5 = C1-4 alkyl, C3-4 unconjugated alkenyl or alkynyl) are prepd. When it is sufficiently exposed to light at a frequency (e.g. 300 nm) and intensity, the acyl-enzyme is photoisomerized from trans to cis, and the enzyme is subsequently activated. 4-Amidinophenyl-(E)-2-hydroxy-4-diethylamino-.alpha.-methylcinnamate hydrochloride (II) was prepd. by treating 4-deithylaminosalicylaldehyde with carbethoxyethylidene triphenylphosphorane and sapond. the ester to acid which was condensed with p-hydroxybenzamidine hydrochloride in DCC/pyridine. An acyl-thrombin was formed by reaction of II with thrombin.

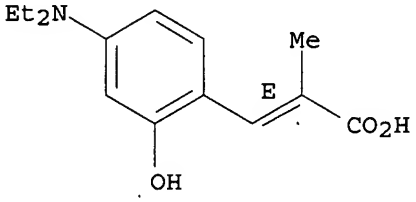
IT **122723-87-9P 127003-61-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, for photoactivatable acyl-enzyme prepn.)
RN 122723-87-9 CAPLUS
CN 2-Propenoic acid, 3-[4-(diethylamino)-2-hydroxyphenyl]-2-methyl-, ethyl ester, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



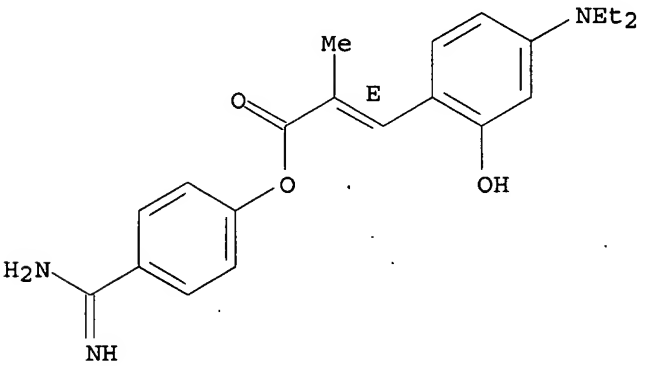
RN 127003-61-6 CAPLUS
CN 2-Propenoic acid, 3-[4-(diethylamino)-2-hydroxyphenyl]-2-methyl-, (E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **122723-86-8P**
RL: PREP (Preparation)
(prepn. of, as intermediate for photoactivatable acyl-enzyme prepn.)
RN 122723-86-8 CAPLUS
CN 2-Propenoic acid, 3-[4-(diethylamino)-2-hydroxyphenyl]-2-methyl-, 4-(aminoiminomethyl)phenyl ester, monohydrochloride, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



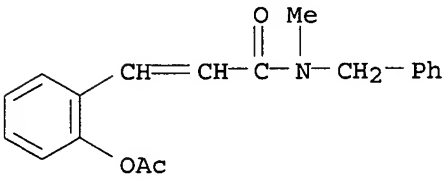
HCl

30 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:429275 CAPLUS
DOCUMENT NUMBER: 131:233454
TITLE: Substituted coumarins as esterase-sensitive prodrug moieties with improved **release** rates
AUTHOR(S): Liao, Yuan; Wang, Binghe
CORPORATE SOURCE: Department of Chemistry, North Carolina State University, Raleigh, NC, 27695-8204, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1999), 9(13), 1795-1800
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

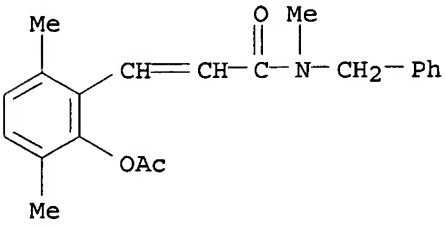
AB A coumarin-based prodrug system for the prepn. of esterase-sensitive prodrugs of amines, peptides, and peptidomimetics has recently been reported by the author. However, the **release** from this prodrug system was undesirably slow for some drug moieties. In this report, the author describes the synthesis and evaluation of several substituted coumarin-based prodrugs of model amines with significantly increased **release** rates.

IT **177708-39-3P 243972-75-0P 243972-76-1P**
243972-77-2P 243972-78-3P 243972-79-4P
RL: PNU (Preparation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(substituted coumarins as esterase-sensitive prodrug moieties with improved **release** rates)

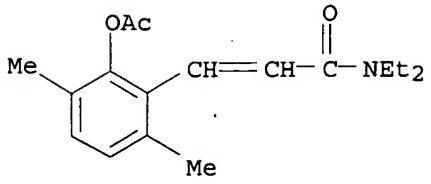
RN 177708-39-3 CAPLUS
CN 2-Propenamide, 3-[2-(acetyloxy)phenyl]-N-methyl-N-(phenylmethyl)- (9CI) (CA INDEX NAME)



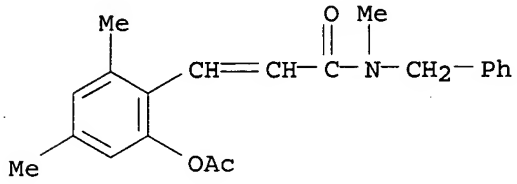
RN 243972-75-0 CAPLUS
CN 2-Propenamide, 3-[2-(acetyloxy)-3,6-dimethylphenyl]-N-methyl-N-(phenylmethyl)- (9CI) (CA INDEX NAME)



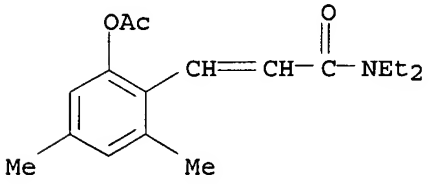
RN 243972-76-1 CAPLUS
CN 2-Propenamide, 3-[2-(acetyloxy)-3,6-dimethylphenyl]-N,N-diethyl- (9CI) (CA INDEX NAME)



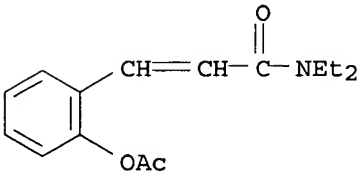
RN 243972-77-2 CAPLUS
CN 2-Propenamide, 3-[2-(acetyloxy)-4,6-dimethylphenyl]-N-methyl-N-(phenylmethyl)- (9CI) (CA INDEX NAME)



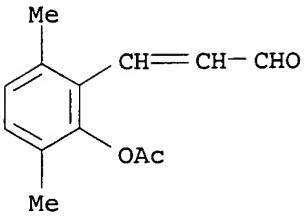
RN 243972-78-3 CAPLUS
CN 2-Propenamide, 3-[2-(acetyloxy)-4,6-dimethylphenyl]-N,N-diethyl- (9CI) (CA INDEX NAME)



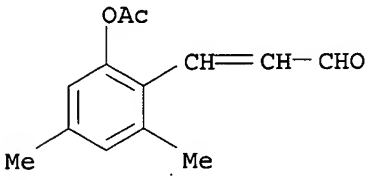
RN 243972-79-4 CAPLUS
CN 2-Propenamide, 3-[2-(acetyloxy)phenyl]-N,N-diethyl- (9CI) (CA INDEX NAME)



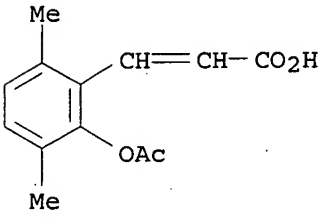
IT **243972-71-6P 243972-72-7P 243972-73-8P 243972-74-9P**
RL: PNU (Preparation, unclassified); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(substituted coumarins as esterase-sensitive prodrug moieties with improved **release** rates)
RN 243972-71-6 CAPLUS
CN 2-Propenal, 3-[2-(acetyloxy)-3,6-dimethylphenyl]- (9CI) (CA INDEX NAME)



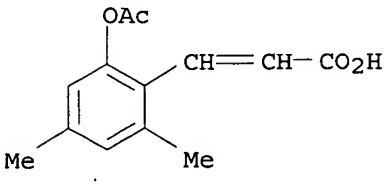
RN 243972-72-7 CAPLUS
CN 2-Propenal, 3-[2-(acetyloxy)-4,6-dimethylphenyl]- (9CI) (CA INDEX NAME)



RN 243972-73-8 CAPLUS
CN 2-Propenoic acid, 3-[2-(acetyloxy)-3,6-dimethylphenyl]- (9CI) (CA INDEX NAME)



RN 243972-74-9 CAPLUS
CN 2-Propenoic acid, 3-[2-(acetyloxy)-4,6-dimethylphenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

30 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:100747 CAPLUS
DOCUMENT NUMBER: 130:144204
TITLE: Modified amino acids as carriers for enhanced delivery of active agents
INVENTOR(S): Leone-Bay, Andrea; Ho, Koc-kan; Sarubbi, Donald J.; Milstein, Sam J.
PATENT ASSIGNEE(S): Emisphere Technologies, Inc., USA
SOURCE: U.S., 27 pp., Cont.-in-part of U.S. Ser. No. 414,654.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 30
PATENT INFORMATION:

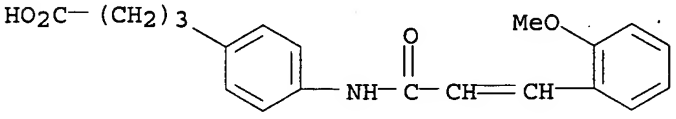
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5866536	A	19990202	US 1997-798033	19970206
US 5650386	A	19970722	US 1995-414654	19950331
CN 1190893	A	19980819	CN 1996-192998	19960401
US 6071510	A	20000606	US 1997-839094	19970423

PRIORITY APPLN. INFO.: US 1995-414654 A2 19950331

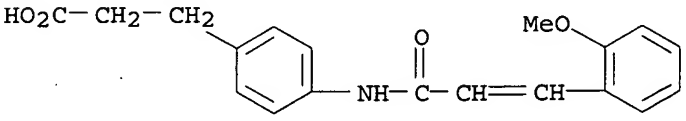
AB Carrier compds., compns., and dosage unit forms which are useful in the delivery of active agents are provided. The present invention provides compds. such as 10-salicyloylaminodecanoic acid (I) for delivery of at least one active agent, including peptides, mucopolysaccharides, carbohydrates, or lipids. I prepd. from 8-aminocaprylic acid and O-acetylsalicyloyl chloride was mixed with recombinant human growth hormone (rhGH) in a phosphate buffer soln. The compn. was orally administered to rats at I 200 mg/kg and rhGH 3 mg/kg and delivery was evaluated by an ELISA assay for rhGH; mean peak serum levels of rhGH was .apprx.60.92 ng/mL as compared to <0.1 ng/mL for control group received a compn. without I.

IT **177653-52-0 177653-65-5 183990-75-2**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modified amino acids as carriers for enhanced delivery of active agents)

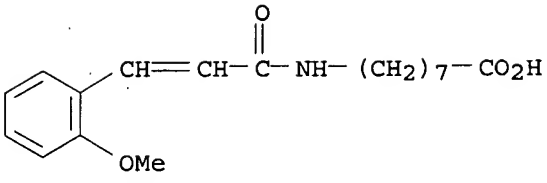
RN 177653-52-0 CAPLUS
CN Benzenebutanoic acid, 4-[[3-(2-methoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



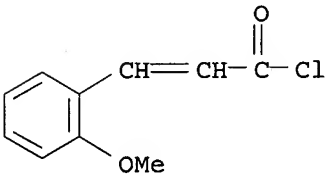
RN 177653-65-5 CAPLUS
CN Benzenepropanoic acid, 4-[[3-(2-methoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



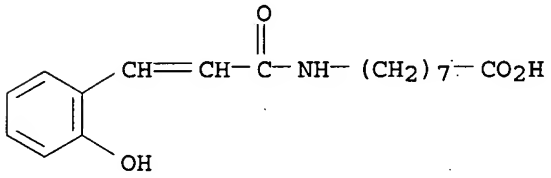
RN 183990-75-2 CAPLUS
CN Octanoic acid, 8-[[3-(2-methoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



IT **15851-91-9**, 2-Methoxycinnamoyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of modified amino acids as carriers for enhanced delivery of active agents)
RN 15851-91-9 CAPLUS
CN 2-Propenoyl chloride, 3-(2-methoxyphenyl)- (9CI) (CA INDEX NAME)



IT **183990-49-0P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of modified amino acids as carriers for enhanced delivery of active agents)
RN 183990-49-0 CAPLUS
CN Octanoic acid, 8-[[3-(2-hydroxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE-FORMAT

L30 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:548547 CAPLUS
DOCUMENT NUMBER: 129:180147
TITLE: Compounds and compositions for delivering active agents
INVENTOR(S): Leone-Bay, Andrea; et al.
PATENT ASSIGNEE(S): Emisphere Technologies, Inc., USA
SOURCE: PCT Int. Appl., 147 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 30
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9834632	A1	19980813	WO 1998-US2619	19980206

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR,

KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG,
US, US, US, US, US, US, US, US, US, US, US, US, US, UZ, VN, YU,
ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,
FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM,
GA, GN, ML, MR, NE, SN, TD, TG

US 5773647	A	19980630	US 1997-796337	19970207	
US 5776888	A	19980707	US 1997-796338	19970207	
US 5804688	A	19980908	US 1997-796339	19970207	
US 5876710	A	19990302	US 1997-796335	19970207	
US 5879681	A	19990309	US 1997-796334	19970207	
US 5939381	A	19990817	US 1997-796340	19970207	
US 5990166	A	19991123	US 1997-797820	19970207	
US 6051561	A	20000418	US 1997-797813	19970207	
US 6060513	A	20000509	US 1997-797817	19970207	
US 6090958	A	20000718	US 1997-797816	19970207	
US 6313088	B1	20011106	US 1997-797100	19970207	
US 6358504	B1	20020319	US 1997-796336	19970207	
AU 9862756	A1	19980826	AU 1998-62756	19980206	
AU 738735	B2	20010927			
EP 1015008	A1	20000705	EP 1998-905042	19980206	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2001513080	T2	20010828	JP 1998-535034	19980206	
NZ 337131	A	20010831	NZ 1998-337131	19980206	
MX 9907290	A	20000531	MX 1999-7290	19990806	
US 2002119910	A1	20020829	US 2000-746548	20001219	
US 2003008900	A1	20030109	US 2001-1731	20011031	
US 6525020	B2	20030225			

PRIORITY APPLN. INFO.:

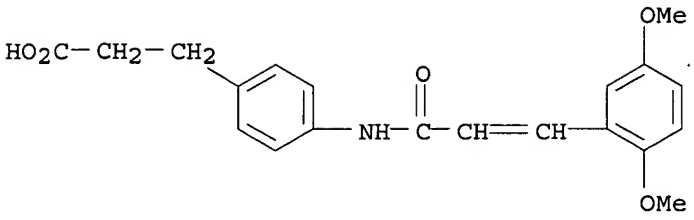
US 1997-796334	A1	19970207
US 1997-796335	A1	19970207
US 1997-796336	A1	19970207
US 1997-796337	A1	19970207
US 1997-796338	A1	19970207
US 1997-796339	A1	19970207
US 1997-796340	A1	19970207
US 1997-796341	A1	19970207
US 1997-797100	A1	19970207
US 1997-797813	A1	19970207
US 1997-797816	A1	19970207
US 1997-797817	A1	19970207
US 1997-797820	A1	19970207
US 1996-17902P	P	19960329
WO 1997-US5128	A2	19970318
EP 1999-117292	A3	19980206
WO 1998-US2619	W	19980206

AB Carrier compds. and compns. which are useful in the delivery of active agents are provided. The carrier compd. can be an amino acid deriv., and the active agent can be a peptide, mucopolysaccharide, carbohydrate, or lipid. Methods of administration, including oral administration, and prepn. are provided as well. For example, an oral soln. contained parathyroid hormone 100 .mu.g, 4-[4-(phenoxyacetyl)aminophenyl]butyric acid (as carrier) 400 mg, and water 1L.

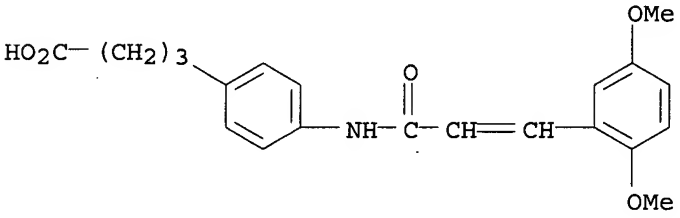
IT **209961-06-8 209961-07-9**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid derivs. as carriers for oral delivery of biol. active agents)

RN 209961-06-8 CAPLUS

CN Benzenepropanoic acid, 4-[[3-(2,5-dimethoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



RN 209961-07-9 CAPLUS
CN Benzenebutanoic acid, 4-[[3-(2,5-dimethoxyphenyl)-1-oxo-2-propenyl]amino]-
(9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:457247 CAPLUS
DOCUMENT NUMBER: 129:113532
TITLE: Compounds and compositions for delivering active agents
INVENTOR(S): Leone-Bay, Andrea; Wang, Eric; Sarubbi, Donald J.; Leipold, Harry
PATENT ASSIGNEE(S): Emisphere Technologies, Inc., USA
SOURCE: U.S., 34 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 30
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5776888	A	19980707	US 1997-796338	19970207
CA 2319672	AA	19980813	CA 1998-2319672	19980206
CA 2319680	AA	19980813	CA 1998-2319680	19980206
WO 9834632	A1	19980813	WO 1998-US2619	19980206
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, US, US, US, US, US, US, US, US, US, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9862756	A1	19980826	AU 1998-62756	19980206
AU 738735	B2	20010927		
EP 993831	A2	20000419	EP 1999-117292	19980206
EP 993831	A3	20010502		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

EP 1015008	A1	20000705	EP 1998-905042	19980206
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1093819	A2	20010425	EP 2000-122704	19980206
EP 1093819	A3	20030514		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001131090	A2	20010515	JP 2000-311231	19980206
JP 2001139494	A2	20010522	JP 2000-311230	19980206
JP 2001513080	T2	20010828	JP 1998-535034	19980206
NZ 337131	A	20010831	NZ 1998-337131	19980206
MX 9907290	A	20000531	MX 1999-7290	19990806
NZ 507275	A	20011130	NZ 2000-507275	20001003
NZ 507276	A	20020201	NZ 2000-507276	20001003

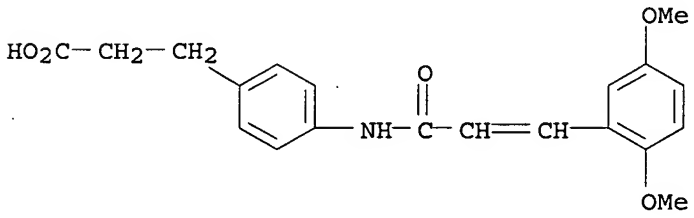
PRIORITY APPLN. INFO.:

US 1997-796334	A	19970207
US 1997-796335	A	19970207
US 1997-796336	A	19970207
US 1997-796337	A	19970207
US 1997-796338	A	19970207
US 1997-796339	A	19970207
US 1997-796340	A	19970207
US 1997-796341	A	19970207
US 1997-797100	A	19970207
US 1997-797813	A	19970207
US 1997-797816	A	19970207
US 1997-797817	A	19970207
US 1997-797820	A	19970207
CA 1998-2279331	A3	19980206
EP 1998-905042	A3	19980206
EP 1999-117292	A3	19980206
JP 1998-535034	A3	19980206
NZ 1998-337131	A1	19980206
WO 1998-US2619	W	19980206

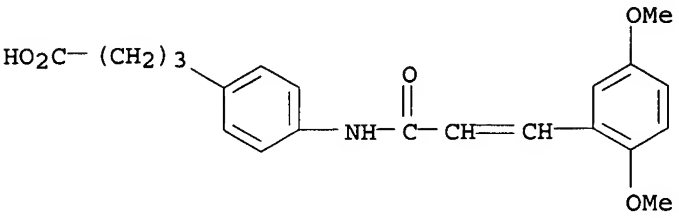
AB Carrier compds. and compns. which are useful in the delivery of active agents are provided. Methods of administration and prepn. are provided as well. Std. methods of prepn. are mentioned for the 193 carrier compds. listed, which primarily are N-(fatty acid) benzamide derivs. Examples are listed for the delivery of parathyroid hormone, recombinant human growth hormone, interferon and the evaluation of heparin in rats.

IT **209961-06-8P 209961-07-9P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of benzamide fatty acid derivs. for delivering active agents)

RN 209961-06-8 CAPLUS
CN Benzenepropanoic acid, 4-[[3-(2,5-dimethoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



RN 209961-07-9 CAPLUS
CN Benzenebutanoic acid, 4-[[3-(2,5-dimethoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:430107 CAPLUS
DOCUMENT NUMBER: 129:113525
TITLE: Compounds and compositions for delivering active agents
INVENTOR(S): Leone-Bay, Andrea; Wang, Eric; Sarubbi, Donald J.; Leipold, Harry
PATENT ASSIGNEE(S): Emisphere Technologies, Inc., USA
SOURCE: U.S., 35 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 30
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5773647	A	19980630	US 1997-796337	19970207
CA 2319672	AA	19980813	CA 1998-2319672	19980206
CA 2319680	AA	19980813	CA 1998-2319680	19980206
WO 9834632	A1	19980813	WO 1998-US2619	19980206
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, US, US, US, US, US, US, US, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9862756	A1	19980826	AU 1998-62756	19980206
AU 738735	B2	20010927		
EP 993831	A2	20000419	EP 1999-117292	19980206
EP 993831	A3	20010502		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1015008	A1	20000705	EP 1998-905042	19980206
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 1093819	A2	20010425	EP 2000-122704	19980206
EP 1093819	A3	20030514		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001131090	A2	20010515	JP 2000-311231	19980206
JP 2001139494	A2	20010522	JP 2000-311230	19980206
JP 2001513080	T2	20010828	JP 1998-535034	19980206
NZ 337131	A	20010831	NZ 1998-337131	19980206
MX 9907290	A	20000531	MX 1999-7290	19990806
NZ 507275	A	20011130	NZ 2000-507275	20001003
NZ 507276	A	20020201	NZ 2000-507276	20001003

PRIORITY APPLN. INFO.: US 1997-796334 A 19970207

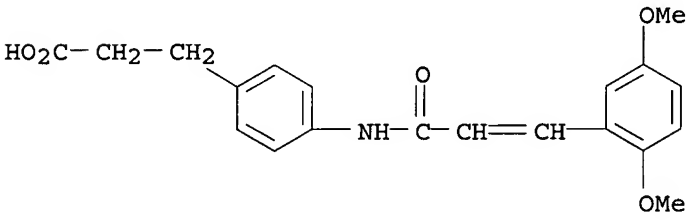
US	1997-796335	A	19970207
US	1997-796336	A	19970207
US	1997-796337	A	19970207
US	1997-796338	A	19970207
US	1997-796339	A	19970207
US	1997-796340	A	19970207
US	1997-796341	A	19970207
US	1997-797100	A	19970207
US	1997-797813	A	19970207
US	1997-797816	A	19970207
US	1997-797817	A	19970207
US	1997-797820	A	19970207
CA	1998-2279331	A3	19980206
EP	1998-905042	A3	19980206
EP	1999-117292	A3	19980206
JP	1998-535034	A3	19980206
NZ	1998-337131	A1	19980206
WO	1998-US2619	W	19980206

AB Carrier compds. and compns. therewith which are useful in the delivery of active agents are provided. Methods of administration and prepn. are provided as well. Std. methods of prepn. are mentioned for the 193 carrier compds. listed, which primarily are N-(fatty acid) benzamide derivs. Examples are listed for the delivery of parathyroid hormone, recombinant human growth hormone, interferon and the evaluation of heparin in rats.

IT **209961-06-8P 209961-07-9P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of benzamide fatty acids for delivering active agents)

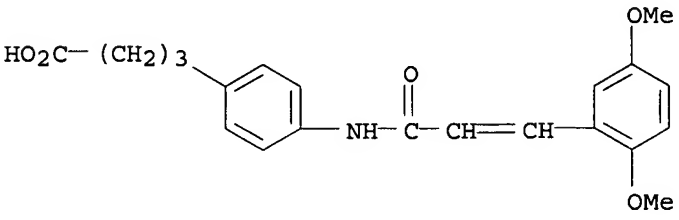
RN 209961-06-8 CAPLUS

CN Benzenepropanoic acid, 4-[[3-(2,5-dimethoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



RN 209961-07-9 CAPLUS

CN Benzenebutanoic acid, 4-[[3-(2,5-dimethoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:274551 CAPLUS

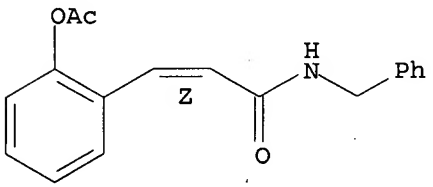
DOCUMENT NUMBER: 129:36081
TITLE: Coumarin-based prodrugs. Part 3: Structural effects on the **release** kinetics of esterase-sensitive prodrugs of amines
AUTHOR(S): Wang, Binghe; Zhang, Huijuan; Zheng, Ailian; Wang, Wei
CORPORATE SOURCE: Department of Chemistry, North Carolina State University, Raleigh, NC, 27695-8204, USA.
SOURCE: Bioorganic & Medicinal Chemistry (1998), 6(4), 417-426
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To study the structural effects on the **release** kinetics of a coumarin-based esterase-sensitive prodrug system, two series of compds. with varying structural features of the ester trigger part and the amine drug part were synthesized. The half-lives of the nine model prodrugs in the presence of porcine liver esterase ranged from .apprx.2 min to 190 min. The steric bulkiness of the acyl group seems to have only a very minor effect on the half-lives of the esterase-triggered **release** of amines from the model prodrugs. The rate of the lactonization depends on the steric and electronic properties of the amine moiety.

IT **208402-14-6P 208402-15-7P 208402-16-8P**
208402-17-9P 208402-18-0P 208402-19-1P
208402-20-4P
RL: PEP (Physical, engineering or chemical process); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)
(structural effects on **release** kinetics of esterase-sensitive coumarin prodrugs of amines)

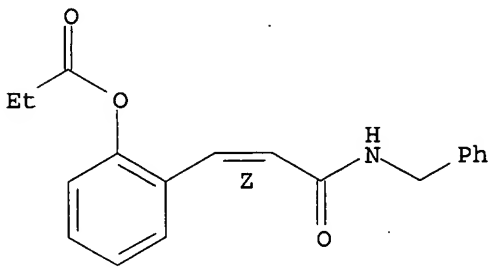
RN 208402-14-6 CAPLUS
CN 2-Propenamide, 3-[2-(acetyloxy)phenyl]-N-(phenylmethyl)-, (2Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 208402-15-7 CAPLUS
CN 2-Propenamide, 3-[2-(1-oxopropoxy)phenyl]-N-(phenylmethyl)-, (2Z)- (9CI) (CA INDEX NAME)

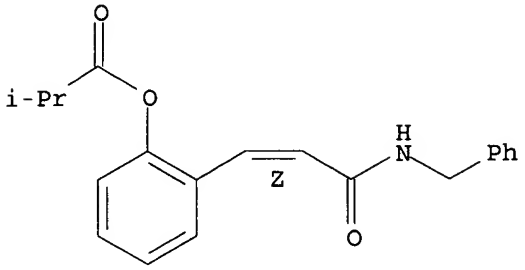
Double bond geometry as shown.



RN 208402-16-8 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1Z)-3-oxo-3-[(phenylmethyl)amino]-1-

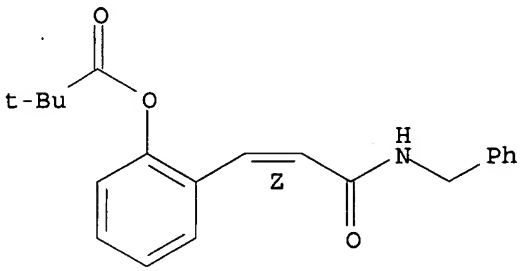
propenyl]phenyl ester (9CI) (CA INDEX NAME)

Double bond geometry as shown.



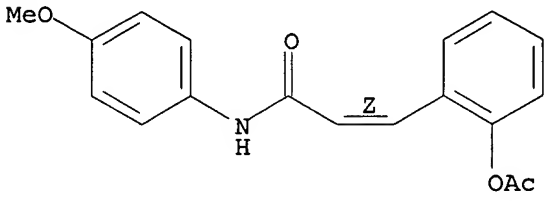
RN 208402-17-9 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 2-[(1Z)-3-oxo-3-[(phenylmethyl)amino]-1-propenyl]phenyl ester (9CI) (CA INDEX NAME)

Double bond geometry as shown.



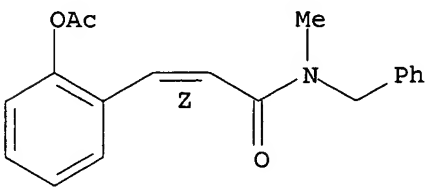
RN 208402-18-0 CAPLUS
CN 2-Propenamide, 3-[2-(acetyloxy)phenyl]-N-(4-methoxyphenyl)-, (2Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



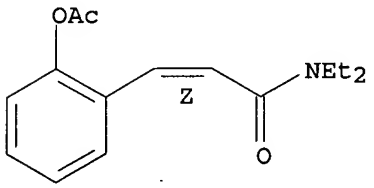
RN 208402-19-1 CAPLUS
CN 2-Propenamide, 3-[2-(acetyloxy)phenyl]-N-methyl-N-(phenylmethyl)-, (2Z)-(9CI) (CA INDEX NAME)

Double bond geometry as shown.



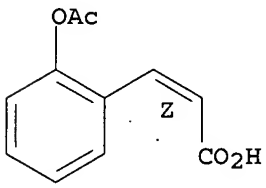
RN 208402-20-4 CAPLUS
CN 2-Propenamide, 3-[2-(acetyloxy)phenyl]-N,N-diethyl-, (2Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



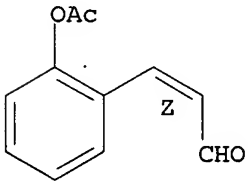
IT **19878-96-7P 208402-01-1P 208402-04-4P**
208402-07-7P 208402-09-9P 208402-11-3P
208402-12-4P 208402-13-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(structural effects on **release** kinetics of esterase-sensitive coumarin prodrugs of amines)
RN 19878-96-7 CAPLUS
CN 2-Propenoic acid, 3-[2-(acetyloxy)phenyl]-, (2Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



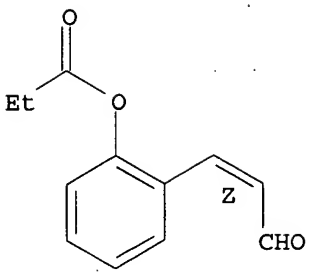
RN 208402-01-1 CAPLUS
CN 2-Propenal, 3-[2-(acetyloxy)phenyl]-, (2Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



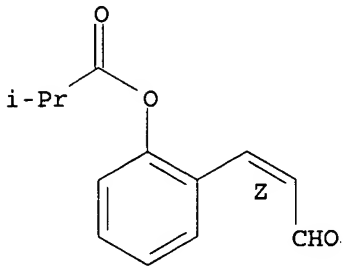
RN 208402-04-4 CAPLUS
CN 2-Propenal, 3-[2-(1-oxopropoxy)phenyl]-, (2Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



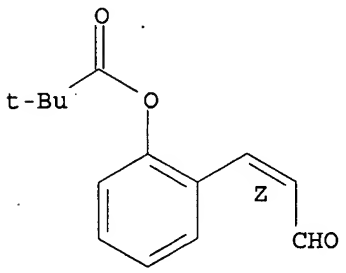
RN 208402-07-7 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1Z)-3-oxo-1-propenyl]phenyl ester (9CI) (CA INDEX NAME)

Double bond geometry as shown.



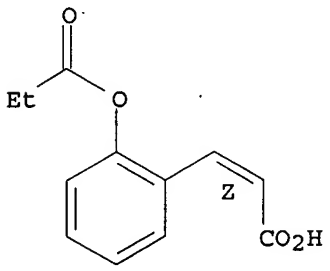
RN 208402-09-9 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 2-[(1Z)-3-oxo-1-propenyl]phenyl ester (9CI) (CA INDEX NAME)

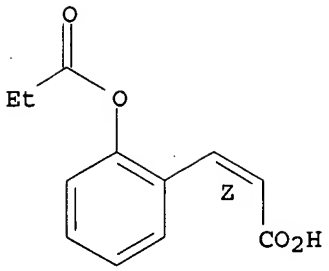
Double bond geometry as shown.



RN 208402-11-3 CAPLUS
CN 2-Propenoic acid, 3-[2-(1-oxopropoxy)phenyl]-, (2Z)- (9CI) (CA INDEX NAME)

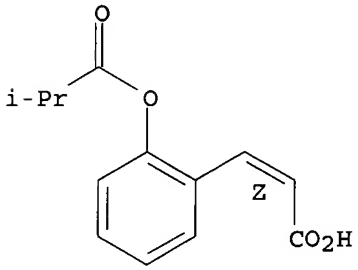
Double bond geometry as shown.





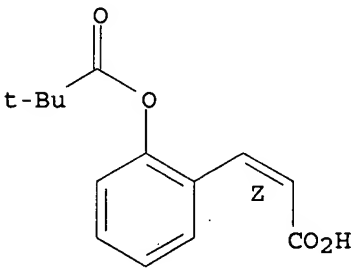
RN 208402-12-4 CAPLUS
CN 2-Propenoic acid, 3-[2-(2-methyl-1-oxopropoxy)phenyl]-, (2Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 208402-13-5 CAPLUS
CN 2-Propenoic acid, 3-[2-(2,2-dimethyl-1-oxopropoxy)phenyl]-, (2Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:672238 CAPLUS
DOCUMENT NUMBER: 127:322800
TITLE: Modified amino acids for **drug delivery**
INVENTOR(S): Leone-Bay, Andrea
PATENT ASSIGNEE(S): Emishphere Technologies, Inc., USA; Leone-Bay, Andrea
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 30
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9736480	A1	19971009	WO 1997-US5128	19970318
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6090958	A	20000718	US 1997-797816	19970207
AU 9725956	A1	19971022	AU 1997-25956	19970318

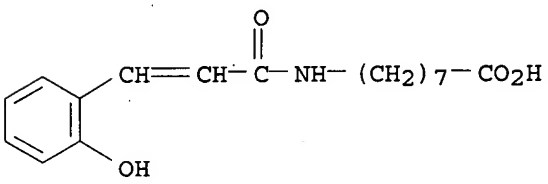
PRIORITY APPLN. INFO.:
US 1996-17902 A1 19960329
US 1996-17902P P 19960329
WO 1997-US5128 A2 19970318

OTHER SOURCE(S): MARPAT 127:322800

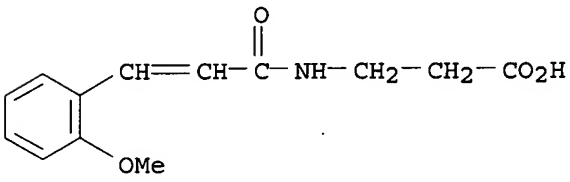
AB Modified amino acid compds. useful in the delivery of active agents are provided. E.g., 2HOC6H4CONH(CH2)7CO2H was prepd. from 8-aminocaprylic acid and O-acetylsalicyloyl chloride. Also examples were give of a nol. of delivery agents enhancement of recombinant human growth hormone bioavailability administered s.c. in rats.

IT **183990-49-0P 197724-89-3P**
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(modified amino acids for **drug delivery**)

RN 183990-49-0 CAPLUS
CN Octanoic acid, 8-[[3-(2-hydroxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)

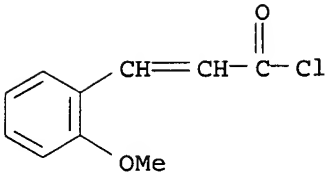


RN 197724-89-3 CAPLUS
CN .beta.-Alanine, N-[3-(2-methoxyphenyl)-1-oxo-2-propenyl]- (9CI) (CA INDEX NAME)

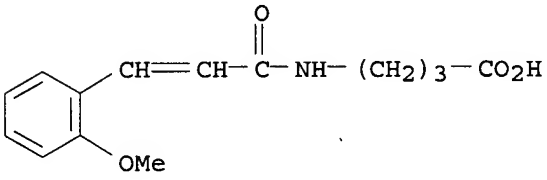


IT **15851-91-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(modified amino acids for **drug delivery**)

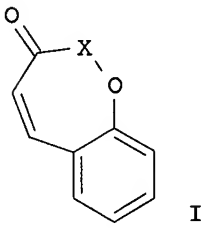
RN 15851-91-9 CAPLUS
CN 2-Propenoyl chloride, 3-(2-methoxyphenyl)- (9CI) (CA INDEX NAME)



IT **197724-92-8P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(modified amino acids for **drug delivery**)
RN 197724-92-8 CAPLUS
CN Butanoic acid, 4-[[3-(2-methoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



L30 ANSWER 14 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:13195 CAPLUS
DOCUMENT NUMBER: 126:118186
TITLE: Coumarin-based prodrugs. 2. Synthesis and bioreversibility studies of an esterase-sensitive cyclic prodrug of DADLE, an opioid peptide
AUTHOR(S): Wang, Binghe; Wang, Wei; Zhang, Huijuan; Shan, Daxian; Smith, Terrill D.
CORPORATE SOURCE: Dep. Chem., North Carolina State Univ., Raleigh, NC, 27695-8204, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1996), 6(23), 2823-2826
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

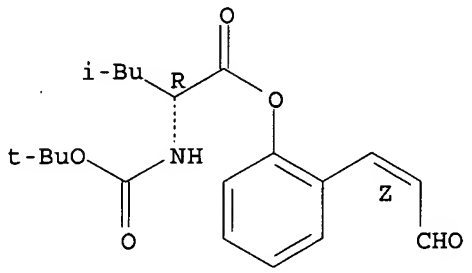
AB A coumarin-based esterase-sensitive cyclic prodrug I (X = -Tyr-D-Ala-Gly-Phe-D-Leu-) of an opioid peptide, DADLE, was prepd. The cyclic prodrug quickly **released** (t1/2 = 761 min) its original peptide, DADLE, upon esterase catalyzed hydrolysis. Such a system can be used for the prepn. of cyclic prodrugs of other biol. active peptides aimed at improving their bioavailability.

IT **185995-99-7P 185996-00-3P 185996-02-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(prepn. of coumarin-based cyclic prodrugs contg. the opioid peptide DADLE)

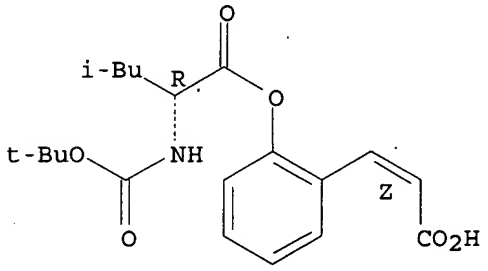
RN 185995-99-7 CAPLUS
CN D-Leucine, N-[(1,1-dimethylethoxy)carbonyl]-, 2-[(1Z)-3-oxo-1-propenyl]phenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 185996-00-3 CAPLUS
CN D-Leucine, N-[(1,1-dimethylethoxy)carbonyl]-, 2-[(1Z)-2-carboxyethenyl]phenyl ester (9CI) (CA INDEX NAME)

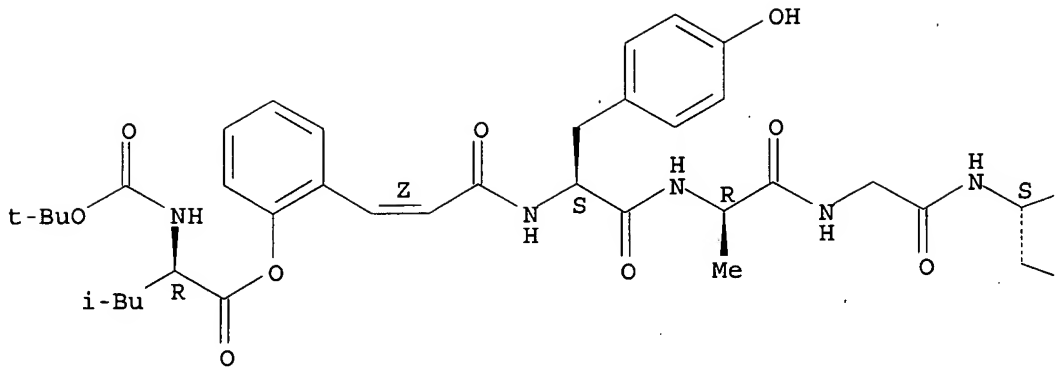
Absolute stereochemistry.
Double bond geometry as shown.



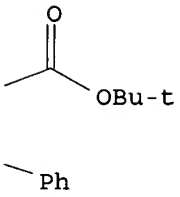
RN 185996-02-5 CAPLUS
CN L-Phenylalanine, N-[(2Z)-3-[2-[[(2R)-2-[[(1,1-dimethylethoxy)carbonyl]amino]-4-methyl-1-oxopentyl]oxy]phenyl]-1-oxo-2-propenyl]-L-tyrosyl-D-alanylglycyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



L30 ANSWER 15 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:87 CAPLUS
DOCUMENT NUMBER: 126:31174
TITLE: Preparation of modified amino acid compounds for delivering active agents
INVENTOR(S): Leone-Bay, Andrea; Ho, Koc-Kan; Sarubbi, Donald J.; Milstein, Sam J.; Press, Jeffery Bruce
PATENT ASSIGNEE(S): Emisphere Technologies, Inc., USA; Leone-Bay, Andrea; Ho, Koc-Kan; Sarubbi, Donald, J.; Milstein, Sam, J.; Press, Jeffery, Bruce
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 30
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9630036	A1	19961003	WO 1996-US4580	19960401
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
US 5650386	A	19970722	US 1995-414654	19950331
CA 2214323	AA	19961003	CA 1996-2214323	19960401
AU 9656629	A1	19961016	AU 1996-56629	19960401

AU 712222	B2	19991104			
EP 817643	A1	19980114	EP 1996-913778	19960401	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI					
BR 9604880	A	19980519	BR 1996-4880	19960401	
JP 2002506418	T2	20020226	JP 1996-529751	19960401	
RU 2203268	C2	20030427	RU 1997-118224	19960401	
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US 6428780	B2	20020806			
US 6346242	B1	20020212	US 2000-499958	20000208	
US 2003045579	A1	20030306	US 2001-38426	20011019	
US 2003078302	A1	20030424	US 2002-142009	20020508	
PRIORITY APPLN. INFO.:			US 1995-414654	A2 19950331	
			US 1995-3111P	P 19950901	
			US 1996-17902P	P 19960329	
			WO 1996-US4580	W 19960401	
			US 1997-798031	A1 19970206	
			US 1999-305506	A1 19990505	
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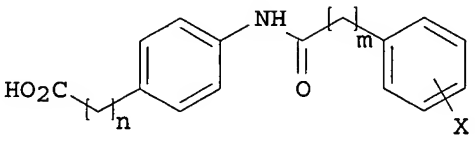
OTHER SOURCE(S): MARPAT 126:31174

GI



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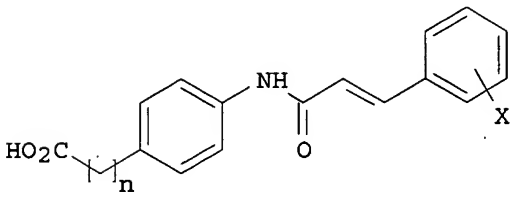

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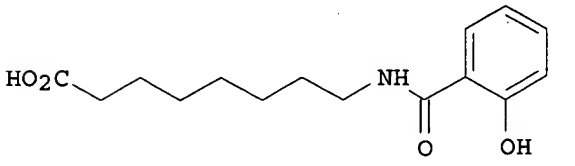


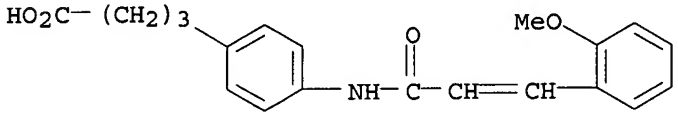
III

AB Modified amino acid compds. [I (n = 0-3; m = 0-4; X = H, halo, OH, etc.), II (n = 0-3; X = 2-F, 3-MeO, 4-Me, etc.), etc.], useful in the delivery of active agents such as, e.g., human growth hormone, interferon, heparin, calcitonin, parathyroid hormone, were prepd. Thus, reaction of 8-aminocaprylic acid with O-acetylsalicyloyl chloride in the presence of 2M aq. NaOH afforded 57% III which was mixed with recombinant growth hormone (rhGH) in a phosphate buffer soln. at pH 7-8 and administered

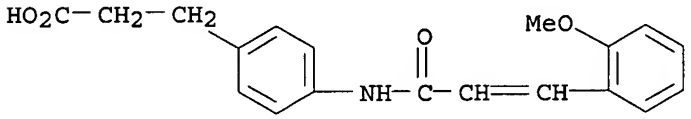
orally to rats at 25 mg/kg of carrier and at 1 mg/kg of rhGH. The mean peak serum level of compd. III was 60.92 ng/mL as compared to < 10 ng/mL for control.

IT **177653-52-0P 177653-65-5P 177653-72-4P**
183990-49-0P 183990-75-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of modified amino acid compds. for delivering active agents)

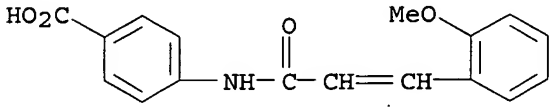
RN 177653-52-0 CAPLUS
CN Benzenebutanoic acid, 4-[[3-(2-methoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



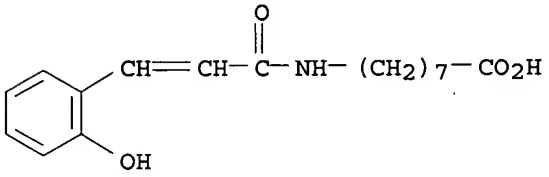
RN 177653-65-5 CAPLUS
CN Benzenepropanoic acid, 4-[[3-(2-methoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



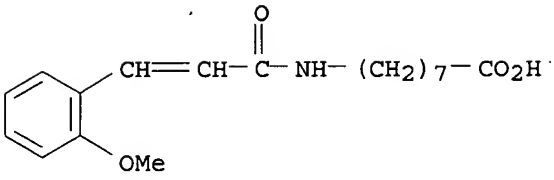
RN 177653-72-4 CAPLUS
CN Benzoic acid, 4-[[3-(2-methoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



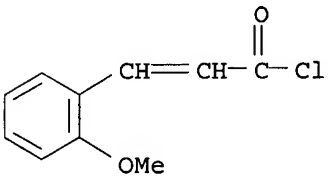
RN 183990-49-0 CAPLUS
CN Octanoic acid, 8-[[3-(2-hydroxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



RN 183990-75-2 CAPLUS
CN Octanoic acid, 8-[[3-(2-methoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



IT **15851-91-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of modified amino acid compds. for delivering active agents)
RN 15851-91-9 CAPLUS
CN 2-Propenoyl chloride, 3-(2-methoxyphenyl)- (9CI) (CA INDEX NAME)



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L9            0 S L4 AND DOXORUBICIN
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L12           0 S L4 AND IRINOTECAN
L13           0 S L4 AND FLUCONAZOLE

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L14             STRUCTURE UPLOADED
L15           3 S L14 SSS SAM

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L16       11790 S PRODRUGS
L17           5 S L16 AND CINNAMATE
L18       10458 S CINNAMATE
L19           2 S L18 AND DOXORUBICIN
L20       14521 S CINNAMIC ACID
L21        5920 S CINNAMYL
L22           2 S L21 AND DOXORUBICIN
L23           2 S L21 AND CAMPTOTHECIN
L24           0 S 2-HYDROXYCINANAMYL
L25           0 S HYDROXYCINANAMYL
L26           0 S 2-HYDROXYCINNAMYL
L27         179 S HYDROXYCINNAMYL
L28           0 S L27 AND DOXORUBICIN
L29           0 S L27 AND PRODRUGS
L30           2 S L27 AND DRUGS
L31          51 S CINNAMYL DERIVATIVES
L32           1 S L31 AND DRUGS
L33        4266 S CINNAMOYL
L34         481 S HYDROXYCINNAMOYL
L35           2 S L34 AND DRUGS
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L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1966:450326 CAPLUS
DOCUMENT NUMBER: 65:50326
ORIGINAL REFERENCE NO.: 65:9440g-h
TITLE: Hemorrhagic syndrome in dogs induced by intravenous thrombin
AUTHOR(S): Girolami, A.; Cliffton, E. E.; Agostino, D.
CORPORATE SOURCE: Cornell Univ. Med. Coll., New York, NY
SOURCE: Thrombosis et Diathesis Haemorrhagica (1966), 16(1-2), 243-56
CODEN: TDHAAT; ISSN: 0340-5338
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Intravenous **administration** of **thrombin** (I) (70 N.I.H. units/kg.) significantly decreased the blood levels of platelets, factor V, factor VIII, and fibrinogen in dogs. I had no effect on factor II and factor VII. Prolongation of glass and silicone clotting times and prothrombin and partial thromboplastin times was also observed. Prothrombin consumption was decreased and thromboplastin generation was defective in all treated animals. Increased fibrinolysis occurred after an initial phase of inhibition following I administration. Increased bleeding from raw **wounds** and from sites of venipuncture was noted in all animals; this increase began 20-30 min. following injection of I and lasted for 60-120 min. In all animals there was a close correlation between bleeding and the decreased level of fibrinogen, factor V, and factor VIII, thereby indicating the importance of these factors in the etiology of the I-induced hemorrhagic syndrome. 45 references.

L6 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1950:57441 CAPLUS
DOCUMENT NUMBER: 44:57441
ORIGINAL REFERENCE NO.: 44:10903d-e
TITLE: Traumatic shock. XVII. Plasma fibrinogen in hemorrhagic shock in the dog
AUTHOR(S): Frank, Edward D.; Frank, Howard A.; Fine, Jacob; Kaufman, Dorothy
CORPORATE SOURCE: Beth Israel Hosp., Boston, MA
SOURCE: American Journal of Physiology (1950), 162, 619-31
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. 43, 6726a. No alteration in plasma fibrinogen concn. was observed in hemorrhagic shock beyond that attributed to hemodiln. or transfusion. A method for complete defibrinogenation in vivo by the intravascular **administration** of **thrombin** is presented as a technique of studying plasma fibrinogen regeneration. Support is given for the concept of liver dysfunction during hemorrhagic hypotension, persisting after restoration of blood vol.

L6 ANSWER 9 OF 15 MEDLINE on STN
ACCESSION NUMBER: 1998173111 MEDLINE
DOCUMENT NUMBER: 98173111 PubMed ID: 9514177
TITLE: Melagatran, an oral active-site inhibitor of thrombin, prevents or delays formation of electrically induced occlusive thrombus in the canine coronary artery.
AUTHOR: Mehta J L; Chen L; Nichols W W; Mattsson C; Gustafsson D; Saldeen T G
CORPORATE SOURCE: Department of Medicine, University of Florida, College of Medicine, and the VA Medical Center, Gainesville 32610, USA.
SOURCE: JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (1998 Mar) 31 (3) 345-51.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980422
Last Updated on STN: 19980422
Entered Medline: 19980416
AB Intravenous **administration** of **thrombin** inhibitors, such as hirudin, has been shown to decrease the frequency of coronary artery reocclusion after thrombolysis. However, recent findings in large clinical trials in patients with unstable angina and myocardial infarction have failed to demonstrate a sustained antithrombotic effect after cessation of drug treatment. These findings indicate a need for a prolonged antithrombotic regimen, preferably an orally active thrombin inhibitor. To test the hypothesis that a regimen consisting of oral thrombin inhibitor will delay or prevent the formation of occlusive clot, anesthetized dogs were given saline (n = 9) or a single dose of a novel active site low-molecular-weight thrombin inhibitor melagatran by nasogastric tube (1.5 mg/kg, n = 6; 2.5 mg/kg, n = 6), and 15 min later, a potent thrombogenic stimulus in the form of anodal current (100 microA) was applied to the intimal surface of the narrowed left anterior descending coronary artery (LAD). All saline-treated dogs developed stable thrombus, indicated by zero flow at 34 +/- 7 min after initiation of direct current. On the other hand, one of the six dogs given high-dose melagatran did not develop thrombotic occlusion of the LAD during the entire 4 h of observation. Mean time to occlusive thrombus formation in 11 other dogs was prolonged 4-5 times as compared with that in the

saline-treated dogs ($p < 0.001$). Spontaneous thrombolysis was observed in three of 11 dogs after initial clot formation. Overall, the coronary artery was patent for 68% (low dose) and 75% (high dose) of the observation period in melagatran-treated dogs (vs. 14% of observation period in saline-treated dogs). Peak plasma concentration was 0.87 +/- 0.22 microM in dogs given low-dose and 1.38 +/- 0.30 microM in dogs given high-dose melagatran. The activated partial thromboplastin time (aPTT) increased 1.5-fold at peak plasma concentration of melagatran. These observations imply (a) thrombin generation plays a critical role in thrombus formation in narrowed coronary arteries, (b) oral melagatran prevents or delays thrombus formation, whereas the aPTT is only modestly prolonged, and (c) the thrombus formed in the presence of melagatran is prone to spontaneous lysis in this canine model of coronary thrombosis.

L6 ANSWER 10 OF 15 MEDLINE on STN
ACCESSION NUMBER: 1998153048 MEDLINE
DOCUMENT NUMBER: 98153048 PubMed ID: 9494029
TITLE: Prolonged thrombin inhibition reduces restenosis after balloon angioplasty in porcine coronary arteries.
AUTHOR: Gallo R; Padurean A; Toschi V; Bichler J; Fallon J T; Chesebro J H; Fuster V; Badimon J J
CORPORATE SOURCE: Cardiovascular Biology Research Laboratory, Mount Sinai School of Medicine, New York, NY, USA.
CONTRACT NUMBER: P50 HL-54469 (NHLBI)
SOURCE: CIRCULATION, (1998 Feb 17) 97 (6) 581-8.
Journal code: 0147763. ISSN: 0009-7322.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980319
Last Updated on STN: 19980319
Entered Medline: 19980310

AB BACKGROUND: Arterial injury after percutaneous transluminal coronary angioplasty (PTCA) triggers acute thrombus formation and thrombin generation. Hirudin, a potent and direct thrombin inhibitor, prevents thrombus formation after arterial injury. Two large clinical trials showed marked reduction in acute clinical events but no long-term benefits in reducing restenosis during short-term **administration** of **thrombin** inhibitors. Our hypothesis is that adequate, maintained thrombin inhibition, by inhibiting all the thrombin-dependent mechanisms, will reduce neointima formation after PTCA. METHODS AND RESULTS: Thirty-six pigs received three different regimens of hirudin: bolus (1 mg/kg), short-term (bolus + 0.7 mg/kg per day for 2 days), and long-term (bolus + 0.7 mg/kg per day for 14 days). The results on neointima formation at 4 weeks after coronary angioplasty were compared with the control group (100 IU heparin/kg bolus). Hirudin was continuously administered for 2 weeks through an infusion pump. In vivo thrombin generation was persistently increased up to 2 weeks after angioplasty. Inhibition of thrombin activity for 14 days reduced luminal narrowing by 40% (58+/-3% versus 35+/-3%; P<.001). No differences were observed among the bolus and short-term hirudin groups and the control group. CONCLUSIONS: Our results indicate that there is a continued, marked thrombin generation that lasts for at least 2 weeks after PTCA. Administration of r-hirudin for 2 weeks significantly reduces neointima formation after PTCA. This observation, if extrapolated to humans, could explain the lack of effect on restenosis observed in the clinical trials with antithrombin agents despite the clear benefits on reducing acute thrombotic complications after PTCA. Therefore an adequate and prolonged **administration** of **thrombin** inhibitors is needed to "passivate" the thrombogenic substrate (disrupted arterial wall) and achieve full benefit of this therapeutic approach.

L6 ANSWER 11 OF 15 MEDLINE on STN
ACCESSION NUMBER: 97057313 MEDLINE
DOCUMENT NUMBER: 97057313 PubMed ID: 8901652
TITLE: Association of heparin-resistant thrombin activity with acute ischemic complications of coronary interventions.
AUTHOR: Oltrona L; Eisenberg P R; Lasala J M; Sewall D J; Shelton M E; Winters K J
CORPORATE SOURCE: II Divisione Cardiologica, Ospedale Niguarda, Milano, Italy.
CONTRACT NUMBER: HL-17646 (NHLBI)
SOURCE: CIRCULATION, (1996 Nov 1) 94 (9) 2064-71.
Journal code: 0147763. ISSN: 0009-7322.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19980206
Entered Medline: 19961206

AB BACKGROUND: Acute thrombosis is thought to contribute to abrupt coronary occlusion during percutaneous coronary revascularization despite the administration of heparin and aspirin. This study was designed to detect the presence of heparin-resistant thrombin activity and to define its relationship to the acute ischemic complications of coronary interventions. METHODS AND RESULTS: Plasma levels of fibrinopeptide A (FPA) and prothrombin fragment 1.2 (F1.2), markers of thrombin and factor Xa activity, respectively, were measured in the coronary sinus with heparin-bonded catheters in 58 patients undergoing coronary interventions. Activated coagulation times were maintained > 300 seconds by the Hemochron method. Mean FPA levels decreased significantly, from 7.0 +/- 0.9 nmol/L before the procedure to 5.2 +/- 0.5 nmol/L after the heparin bolus and to 2.9 +/- 0.2 nmol/L after the procedure (P = .0001). In 26 patients (45%), FPA levels remained above the threshold for suppression angioplasty of thrombin activity determined during angiography in 7 patients without coronary artery **disease** (> 3.0 nmol/L). FPA concentrations after coronary interventions were increased in patients with intracoronary thrombus (P = .01), abrupt coronary occlusion (P = .06), postprocedural non-Q-wave myocardial infarction (P = .04), and clinically unsuccessful procedures (P = .04). F1.2 levels were relatively low before the procedures and did not change significantly. CONCLUSIONS: Heparin **administration** suppresses **thrombin** activity in most but not all patients undergoing coronary interventions. Heparin-resistant thrombin activity is associated with angiographic evidence of intracoronary thrombus and ischemic complications of coronary interventions.

L6 ANSWER 12 OF 15 MEDLINE on STN
ACCESSION NUMBER: 93223634 MEDLINE
DOCUMENT NUMBER: 93223634 PubMed ID: 8467758
TITLE: Effect of a synthetic leukocyte elastase inhibitor on thrombin-induced pulmonary edema in the rat.
AUTHOR: Ahn C M; Sandler H; Glass M; Saldeen T
CORPORATE SOURCE: Department of Internal Medicine, Yongsei University College of Medicine, Seoul Korea.
SOURCE: EXPERIMENTAL LUNG RESEARCH, (1993 Mar-Apr) 19 (2) 125-35.
Journal code: 8004944. ISSN: 0190-2148.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199305
ENTRY DATE: Entered STN: 19930521
Last Updated on STN: 20000303

Entered Medline: 19930512

AB The effect of a synthetic leukocyte elastase inhibitor on thrombin-induced pulmonary edema was studied in rats. The chloromethylketone human neutrophil elastase inhibitor, ICI 200,355, blunted rat leukocyte elastase activity in rat lung tissue. **Administration** of **thrombin** produced a significant increase ($p < .01$) in lung weight. The wet weight to dry weight ratio (WW/DW) and relative water contents were also significantly elevated ($p < .01$). Pretreatment with ICI 200,355 (200 micrograms/kg h-1) resulted in significant reductions ($p < .05$) in lung weight and a tendency to decrease WW/DW and water content compared with animals given thrombin alone. It is possible that the elastase inhibitor effectively reduced the rate of thrombin-induced pulmonary edema by attenuation of increased vascular permeability.

L6 ANSWER 13 OF 15 MEDLINE on STN
ACCESSION NUMBER: 90102204 MEDLINE
DOCUMENT NUMBER: 90102204 PubMed ID: 2603849
TITLE: Experimental retinal vein obstruction induced by transadventitial **administration** of **thrombin** in the rabbit.
AUTHOR: Sakuraba T
SOURCE: NIPPON GANKA GAKKAI ZASSHI. ACTA SOCIETATIS OPHTHALMOLOGICAE JAPONICAE, (1989 Oct) 93 (10) 978-85. Journal code: 7505716. ISSN: 0029-0203.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199002
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19900205

AB Retinal venous obstruction with typical flame-shaped hemorrhage was experimentally produced in the rabbit by transadventitial dropping of thrombin on target vessels by vitreous surgery techniques. The changes were studied ophthalmoscopically, light and electron microscopically. Flame-shaped retinal hemorrhage appeared within 24hr after the maneuver of thrombin dropping, following the initial appearance of small hemorrhage during the first 8 to 12hr of the experiment. Microscopic study revealed the process of subendothelial fibrin-thrombus formation in the target venules. Thrombus formation began 6hr after dropping of thrombin and vascular lumina were markedly narrowed by 24hr. No endothelial defect was found in the target venule between 6 and 12hrs after thrombin dropping, though fibrin-platelet thrombi were often found in the lumina of the venules. In the arteriole, on the other hand, intramural thrombus was seen only in the earlier stage, not later than 6hr after dropping of thrombin, in the area peripheral to the site of dropping. These findings suggested the possibility of transmural effects of thrombin as well as participation of arterioles in thrombogenesis, and supports the usefulness of this experimental model for the study of retinal venous obstruction.

L6 ANSWER 14 OF 15 MEDLINE on STN
ACCESSION NUMBER: 90101284 MEDLINE
DOCUMENT NUMBER: 90101284 PubMed ID: 2603331
TITLE: Dyspnea in aging rats due to disseminated intravascular coagulation (DIC).
AUTHOR: Carthew P; Aldred P; Hill R J; Riley J; Edwards R E
CORPORATE SOURCE: MRC Toxicology Unit, Carshalton, Surrey, England.
SOURCE: VETERINARY PATHOLOGY, (1989 Nov) 26 (6) 505-9. Journal code: 0312020. ISSN: 0300-9858.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199002
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19900207

AB During an 18-month oncogenicity study using rats, approximately 10% of the animals developed a form of respiratory distress very similar to that seen in the terminal stages of chronic respiratory **disease**, commonly associated with Mycoplasma pulmonis infection. Investigation of the lungs of the affected rats revealed not only that they did not have the consolidation usually associated with chronic respiratory **disease** , but they also appeared macroscopically normal. Further investigation of a number of cases revealed systemic intravascular thrombus formation of the type usually referred to as disseminated intravascular coagulation. Using an antiserum to fibrin we have demonstrated the presence of intravascular fibrin deposits in the lungs of the affected rats and have shown them to be the same as experimentally induced intravascular fibrin deposits induced in rat lungs by the **administration** of **thrombin** after blocking the fibrinolytic system. This is the first example of such a phenomenon being recorded in aging rats.

L6 ANSWER 15 OF 15 MEDLINE on STN
ACCESSION NUMBER: 83126042 MEDLINE
DOCUMENT NUMBER: 83126042 PubMed ID: 7159237
TITLE: [Structural and metabolic changes in the contractile myocardium in experimental acute pulmonary heart **disease** of vascular origin].
Strukturno-metabolicheskie izmeneniia sokratitel'nogo miokarda pri eksperimental'nom ostrom legochnom serdtse sosudistogo geneza.
AUTHOR: Vinogradov S A; Shpilevskii I I; Galakhin K A; Kolbasin P N
SOURCE: ARKHIV PATOLOGII, (1982) 44 (11) 44-51.
Journal code: 0370604. ISSN: 0004-1955.
PUB. COUNTRY: USSR
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198303
ENTRY DATE: Entered STN: 19900318
Last Updated on STN: 19900318
Entered Medline: 19830317

AB The myocardium of 37 rabbits with a fulminant (Group 1) and acute (Group 2) course of experimental acute pulmonary heart of vascular genesis produced by intravenous **administration** of **thrombin** in subcutaneous administration of histamine was studied. The control consisted of 9 hearts of rabbits sacrificed by intravenous novocain injection. Combined methods were used to examine the myocardium, including special staining methods suitable for detection of early cardiomyocyte damage, polarization and electron microscopy, histoenzymological methods, and histostereometry. The volumetric density of focal alterations in comparison of the results between groups both for the heart as a whole and for both its parts was found to be statistically significantly higher than that in the controls. Similar results were obtained in the right to left ventricle ratio. No significant differences in the values compared were found in the controls. The volumetric density of focal lesions reached the maximum values in Group 2 by 24 hours in the right parts. The results indicate that the alterative form of cardiac insufficiency underlies sudden death in acute pulmonary heart of the vascular genesis.

=> d his

(FILE 'HOME' ENTERED AT 06:40:55 ON 09 AUG 2003)

FILE 'CAPLUS, MEDLINE' ENTERED AT 06:41:02 ON 09 AUG 2003

L1	0	S	ADMINSTRATION OF THROMBIN
L2	89	S	ADMINISTRATION OF THROMBIN
L3	1	S	L2 AND PRODRUGS
L4	1	S	L2 AND WOUNDS
L5	0	S	L2 AND INFECTIONS
L6	15	S	L2 AND DISEASE

L6 ANSWER 1 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:76643 CAPLUS
DOCUMENT NUMBER: 138:131108
TITLE: Use of thrombin inhibitors for the treatment of arthritis
INVENTOR(S): Hauel, Norbert; Wienen, Wolfgang
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma KG, Germany
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003007984	A1	20030130	WO 2002-EP7679	20020710
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10133786	A1	20030206	DE 2001-10133786	20010716

PRIORITY APPLN. INFO.: DE 2001-10133786 A 20010716
AB The invention concerns the **administration** of **thrombin** inhibitors for the prevention and treatment of rheumatic arthritis that inhibit only the catalytic domains of thrombin but do not block the exosite domains of thrombin. Addnl., the applied thrombin inhibitor is also a trypsin inhibitor, the Ki value for thrombin is 200 nm, for trypsin 500 nm. The thrombin inhibitor is selected from the group of BIBR 953, its prodrug and Melagatran and its prodrug. The thrombin inhibitor can be used in combination with analgesics and antirheumatic agents. The induction of arthritis in female mice and treatment with BIBR 1048 is presented.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:80326 CAPLUS
DOCUMENT NUMBER: 130:306319
TITLE: The effect of rt-PA alone and in combination with thrombin inhibitors in a model of cerebrovascular thrombosis in the rabbit
AUTHOR(S): Liu, Juntian; Paul, William; Powing, Max J.; Page, Clive P.
CORPORATE SOURCE: Department of Pharmacology, Xi'an Medical University, Xi'an, 710061, Peop. Rep. China
SOURCE: Journal of Xi'an Medical University (1998), 10(2), 97-102
CODEN: JXMUEC; ISSN: 1000-923X
PUBLISHER: Xi'an Medical University
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sustained accumulation of111 indium-labeled platelets is induced in the cerebral vasculature of rabbits by bolus intracarotid (i.c.) **administration** of **thrombin** (90 U/kg). Bolus i.c. injection of the fibrinolytic, recombinant tissue plasminogen activator

(rt-PA), 1 min after thrombin, produced significant inhibition of the platelet accumulation, albeit substantially less than that produced by 1 min pretreatment. Hirulog, PPACK and rt-PA alone had no direct effect on the basal circulating levels of111 In-labeled platelets in the pulmonary or cranial vasculature at the doses used. Hirulog and PPACK did not enhance the ability of infusion of a threshold dose of rt-PA to decrease an established cerebrovascular thrombosis, whereas Defibrotide plus rt-PA produced a significant redn. on accumulated platelets. These results suggest that fibrin deposition plays the important role in the induction and maintenance of the sustained cerebral platelet accumulation induced by thrombin in this model and Defibrotide can enhance the pro-fibrinolytic effect of rt-PA although this property is not shared by direct thrombin inhibitors. The sustained platelet accumulation in the cranial vasculature in this model does not appear to be a result of continued generation of endogenous thrombin.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1998:145826 CAPLUS

DOCUMENT NUMBER: 128:239222

TITLE: Prolonged thrombin inhibition reduces restenosis after balloon angioplasty in porcine coronary arteries

AUTHOR(S): Gallo, Richard; Padurean, Adrian; Toschi, Vincenzo; Bichler, Johan; Fallon, John T.; Chesebro, James H.; Fuster, Valentin; Badimon, Juan J.

CORPORATE SOURCE: Cardiovascular Biology Research Laboratory, Mount Sinai School of Medicine, New York, NY, USA

SOURCE: Circulation (1998), 97(6), 581-588
CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Arterial injury after percutaneous transluminal coronary angioplasty (PTCA) triggers acute thrombus formation and thrombin generation. Hirudin, a potent and direct thrombin inhibitor, prevents thrombus formation after arterial injury. Two large clin. trials showed marked redn. in acute clin. events but no long-term benefits in reducing restenosis during short-term **administration** of **thrombin** inhibitors. Our hypothesis is that adequate, maintained thrombin inhibition, by inhibiting all the thrombin-dependent mechanisms, will reduce neointima formation after PTCA. Thirty-six pigs received three different regimens of hirudin: bolus (1 mg/kg), short-term (bolus+0.7 mg/kg per day for 2 days), and long-term (bolus+0.7 mg/kg per day for 14 days). The results on neointima formation at 4 wk after coronary angioplasty were compared with the control group (100 IU heparin/kg bolus). Hirudin was continuously administered for 2 wk through an infusion pump. In vivo thrombin generation was persistently increased up to 2 wk after angioplasty. Inhibition of thrombin activity for 14 days reduced luminal narrowing by 40% (58.+-.3% vs. 35.+-.3%; P<.001). No differences were obsd. among the bolus and short-term hirudin groups and the control group. Our results indicate that there is a continued, marked thrombin generation that lasts for at least 2 wk after PTCA. Administration of r-hirudin for 2 wk significantly reduces neointima formation after PTCA. This observation, if extrapolated to humans, could explain the lack of effect on restenosis obsd. in the clin. trials with antithrombin agents despite the clear benefits on reducing acute thrombotic complications after PTCA. Therefore an adequate and prolonged **administration** of **thrombin** inhibitors is needed to "passivate" the thrombogenic substrate (disrupted arterial wall) and achieve full benefit of this therapeutic approach.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:71893 CAPLUS
DOCUMENT NUMBER: 124:135321
TITLE: Beneficial effects of a leukotriene receptor antagonist on thrombin-induced pulmonary edema in the rat
AUTHOR(S): Ahn, C. Min.; Sandler, H.; Saldeen, T.
CORPORATE SOURCE: Dep. Forensic Medicine, Univ. Uppsala, Swed.
SOURCE: Prostaglandins, Leukotrienes and Essential Fatty Acids (1995), 53(6), 433-8
CODEN: PLEAEU; ISSN: 0952-3278
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of a selective leukotriene receptor antagonist, the peptide ICI 198,615, on thrombin-induced pulmonary edema was studied in rats. **Administration** of **thrombin** produced a significant increase in lung wt. ($p<0.05$), wet wt. to dry wt. ratio (WW/DW; $p<0.05$), and relative lung water content ($p<0.05$). These increases were all significantly reduced ($p<0.05$) by ICI 198,615 (bolus 15 mg/kg, infusion 15 mg/kg/h). Thrombin infusion caused a significant increase in myeloperoxidase activity in the lung tissue ($p<0.05$). This increase was further accentuated by ICI 198,615, indicating that the effect of this antagonist is not due to redn. of leukocyte infiltration in the lungs. The results thus show that a leukotriene receptor antagonist effectively counteracts the increase in lung vascular permeability to protein caused by thrombin, and indicate that leukotrienes are important mediators of thrombin-induced pulmonary edema in the rat.

L6 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:95183 CAPLUS
DOCUMENT NUMBER: 120:95183
TITLE: The effect of defibrotide on thromboembolism in the pulmonary vasculature of mice and rabbits and in the cerebral vasculature of rabbits
AUTHOR(S): Paul, W.; Gresele, P.; Momi, S.; Bianchi, G.; Page, C. P.
CORPORATE SOURCE: King's Coll., Univ. London, London, SW3 6LX, UK
SOURCE: British Journal of Pharmacology (1993), 110(4), 1565-71
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Administration of bovine thrombin (100 u kg-1) into the carotid artery of rabbits induces a sustained accumulation of 111Indium-labeled platelets within the cranial vasculature over the subsequent 3 h. Intracarotid (i.c.) administration of defibrotide (64 mg kg-1 bolus plus 64 mg kg-1 h-1 for 1 h) prior to i.c. thrombin (d100 u kg-1) significantly reduces the ability of thrombin to induce cranial thromboembolism in rabbits. I.v. **administration** of **thrombin** (20 u kg-1) in rabbits induces a reversible accumulation of radiolabeled platelets into the thoracic circulation which is significantly reduced by i.v. administration of defibrotide (64 mg kg-1 bolus plus 64 mg kg-1 h-1 for 1 h) prior to i.v. thrombin. In contrast, platelet accumulation in response to ADP (ADP; 20 .mu.g kg-1, i.v.) or platelet activating factor (PAF; 50 ng kg-1, i.v.) is not significantly affected by this treatment. I.v. administration of the nitric oxide (NO)-synthase inhibitor NG-nitro-L-arginine Me ester (L-NAME; 10 mg kg-1) potentiates platelet accumulation induced by low dose thrombin (10 u kg-1, i.v.) within the pulmonary vasculature of rabbits. The potentiated response is significantly abrogated following pretreatment with defibrotide (64 mg kg-1 bolus plus 64 mg kg-1 h-1 for 1 h, i.v.). I.v. injection of human thrombin (1250 u kg-1) to mice induces death within the majority of animals which is significantly reduced by pretreatment with defibrotide

L7 ANSWER 1 OF 27 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:76643 CAPLUS
DOCUMENT NUMBER: 138:131108
TITLE: Use of thrombin inhibitors for the **treatment** of arthritis
INVENTOR(S): Hauel, Norbert; Wienen, Wolfgang
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma KG, Germany
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003007984	A1	20030130	WO 2002-EP7679	20020710
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10133786	A1	20030206	DE 2001-10133786	20010716

PRIORITY APPLN. INFO.: DE 2001-10133786 A 20010716
AB The invention concerns the **administration** of **thrombin** inhibitors for the prevention and **treatment** of rheumatic arthritis that inhibit only the catalytic domains of thrombin but do not block the exosite domains of thrombin. Addnl., the applied thrombin inhibitor is also a trypsin inhibitor, the Ki value for thrombin is 200 nm, for trypsin 500 nm. The thrombin inhibitor is selected from the group of BIBR 953, its prodrug and Melagatran and its prodrug. The thrombin inhibitor can be used in combination with analgesics and antirheumatic agents. The induction of arthritis in female mice and **treatment** with BIBR 1048 is presented.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 27 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:860242 CAPLUS
DOCUMENT NUMBER: 135:14086
TITLE: Intrathecal **administration** of **thrombin** inhibitor ameliorates cerebral vasospasm: Use of a drug delivery system releasing hirudin
AUTHOR(S): Kudo, Akira; Suzuki, Michiyasu; Kubo, Yoshitaka; Watanabe, Mikio; Yoshida, Kenji; Doi, Mamoru; Kuroda, Kiyoshi; Ogawa, Akira
CORPORATE SOURCE: Department of Neurosurgery, Iwate Medical University School of Medicine, Morioka, 020, Japan
SOURCE: Cerebrovascular Diseases (Basel, Switzerland) (2000), 10(6), 424-430
CODEN: CDISE7; ISSN: 1015-9770
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The role of thrombin as a spasmogen after subarachnoid hemorrhage was evaluated using the intrathecally administered thrombin inhibitor hirudin,

released from a drug delivery system (DDS) based on collagen in a canine vasospasm model. The DDS was implanted into the cisterna magna with autologous blood in the hirudin **treated** group. The redn. in the angiog. diam. of the basilar artery was only 19% in the hirudin-**treated** group on day 7, showing a significant difference between hirudin-**treated** and nontreated groups ($p < 0.01$). These results suggest that thrombin is an important cause of vasospasm. The collagen DDS has great potential for **treatment** in the cerebrospinal fluid milieu.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 27 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:489597 CAPLUS
DOCUMENT NUMBER: 132:226
TITLE: The effects of argatroban on thrombin-induced cerebrovascular thromboembolism in rabbits
AUTHOR(S): Liu, Juntian; Paul, W.; Page, C. P.
CORPORATE SOURCE: Department of Pharmacology, Xi'an Medical University, Xi'an, 710061, Peop. Rep. China
SOURCE: Journal of Xi'an Medical University (1999), 11(1), 26-30
CODEN: JXMUEC; ISSN: 1000-923X
PUBLISHER: Xi'an Medical University
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sustained accumulation of 111In-labeled platelets was induced in the cerebral vasculature of rabbits by bolus intracarotid **administration** of **thrombin**. Bolus intracarotid injection of the thrombin inhibitor argatroban, 1 min before thrombin, reduced platelet accumulation by >90%, whereas when argatroban was administered 1 min after thrombin there was no significant effect. Intracarotid infusion of argatroban (at a dose which was effective when administered prior to thrombin), commencing 30 min after thrombin, produced no significant redn. in entrapped platelets. Argatroban did not enhance the ability of infusion of a threshold dose of recombinant tissue plasminogen activator (rt-PA) to decrease an established cerebrovascular thrombosis. These results suggest that pretreatment with the thrombin inhibitor argatroban can inhibit thrombin-induced cerebral thromboembolism in rabbits but cannot enhance the profibrinolytic effect of rt-PA.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 27 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:215220 CAPLUS
DOCUMENT NUMBER: 131:13680
TITLE: Pro- and anti-inflammatory actions of thrombin: a distinct role for proteinase-activated receptor-1 (PAR1)
AUTHOR(S): Vergnolle, Nathalie; Hollenberg, Morley D.; Wallace, John L.
CORPORATE SOURCE: Gastrointestinal Research Group, Departments of Pharmacology & Therapeutics and Medicine, Faculty of Medicine, University of Calgary, Calgary, AB, T2N 4N1, Can.
SOURCE: British Journal of Pharmacology (1999), 126(5), 1262-1268
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thrombin has well characterized pro-inflammatory actions that have recently been suggested to occur via activation of its receptor, proteinase-activated receptor-1 (PAR1). In the present study, we have

compared the effects of thrombin to those of two peptides that selectively activate the PAR1 receptor, in a rat hindpaw edema model. We have also examd. whether or not thrombin can exert anti-inflammatory activity in this model. Both thrombin and the two PAR1 activating peptides induced significant edema in the rat hindpaw following subplantar injection. The edema induced by thrombin was abolished by pre-incubation with hirudin, and was markedly reduced in rats in which mast cells were depleted through **treatment** with compd. 48/80 and in rats pretreated with indomethacin. In contrast, administration of the PAR1 activating peptides produced an edema response that was not reduced by indomethacin and was only slightly reduced in rats pretreated with compd. 48/80. Co-**administration** of **thrombin** together with a PAR1 activating receptor resulted in a significantly smaller edema response than that seen with the PAR1 activating peptide alone. This anti-inflammatory effect of thrombin was abolished by pre-incubation with hirudin. These results demonstrate that the pro-inflammatory effects of thrombin occur through a mast-cell-dependent mechanism i.e., at least in part, independent of activation of the PAR1 receptor. Moreover, thrombin is able to exert anti-inflammatory effects that are also unrelated to the activation of PAR1.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 27 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1998:162418 CAPLUS

DOCUMENT NUMBER: 128:265942

TITLE: Melagatran, an oral active-site inhibitor of thrombin, prevents or delays formation of electrically induced occlusive thrombus in the canine coronary artery

AUTHOR(S): Mehta, Jawahar L.; Chen, Liying; Nichols, Wilmer W.; Mattsson, Christer; Gustafsson, David; Saldeen, Tom G. P.

CORPORATE SOURCE: Department of Medicine, College of Medicine, University of Florida, Gainesville, FL, 32610, USA

SOURCE: Journal of Cardiovascular Pharmacology (1998), 31(3), 345-351
CODEN: JCPCDT; ISSN: 0160-2446

PUBLISHER: Lippincott-Raven Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB I.v. **administration** of **thrombin** inhibitors, such as hirudin, has been shown to decrease the frequency of coronary artery reocclusion after thrombolysis. However, recent findings in large clin. trials in patients with unstable angina and myocardial infarction have failed to demonstrate a sustained antithrombotic effect after cessation of drug **treatment**. These findings indicate a need for a prolonged antithrombotic regimen, preferably an orally active thrombin inhibitor. To test the hypothesis that a regimen consisting of oral thrombin inhibitor will delay or prevent the formation of occlusive clot, anesthetized dogs were given saline or a single dose of a novel active site low-mol.-wt. thrombin inhibitor melagatran by nasogastric tube (1.5 mg/kg,; 2.5 mg/kg), and 15 min later, a potent thrombogenic stimulus in the form of anodal current (100 .mu.A) was applied to the intimal surface of the narrowed left anterior descending coronary artery (LAD). All saline-**treated** dogs developed stable thrombus, indicated by zero flow at 34 min after initiation of d.c. One of the six dogs given high-dose melagatran did not develop thrombotic occlusion of the LAD during the entire 4 h of observation. Mean time to occlusive thrombus formation in 11 other dogs was prolonged 4-5 times as compared with that in the saline-**treated** dogs. Spontaneous thrombolysis was obsd. in three of 11 dogs after initial clot formation. Overall, the coronary artery was patent for 68% (low dose) and 75% (high dose) of the observation period in melagatran-**treated** dogs (vs. 14% of observation period in saline-**treated** dogs). Peak plasma concn.

was 0.87 .mu.M in dogs given low-dose and 1.38 .mu.M in dogs given high-dose melagatran. The activated partial thromboplastin time (aPTT) increased 1.5-fold at peak plasma concn. of melagatran. These observations imply (a) thrombin generation plays a crit. role in thrombus formation in narrowed coronary arteries, (b) oral melagatran prevents or delays thrombus formation, whereas the aPTT is only modestly prolonged, and (c) the thrombus formed in the presence of melagatran is prone to spontaneous lysis in this canine model of coronary thrombosis.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:535201 CAPLUS
DOCUMENT NUMBER: 127:171356
TITLE: Intra urinary bladder **administration** of **thrombin** in massive bleeding hemostasis
AUTHOR(S): Li, Zongliang; Yang, Huazhang; Cheng, Ying; Zhang, Honge
CORPORATE SOURCE: Guangdong Provincial People's Hospital, Canton, 510080, Peop. Rep. China
SOURCE: Guangdong Yixue (1997), 18(5), 345
CODEN: GUYIEG; ISSN: 1001-9448
PUBLISHER: Guangdongsheng Yixue Qingbao Yanjiuso
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Urinary bladder massive bleeding because of carcinoma in 3 cases and hemorrhagic cystitis in 1 case were **treated** by intra bladder **administration** of **thrombin** and showed satisfactory results. 4000 U of thrombin in 20-40 mL normal saline was retained in the bladder for 2 h b.i.d. for 3 days. 4 Patients obtained hemostasis within 1-5 days.

L7 ANSWER 7 OF 27 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:225890 CAPLUS
DOCUMENT NUMBER: 122:28930
TITLE: Calcium-mobilizing agonists stimulate anion fluxes in cultured endothelial cells from human umbilical vein
AUTHOR(S): White, C. R.; Brock, T. A.
CORPORATE SOURCE: Department Medicine, University Alabama at Birmingham, Birmingham, AL, 35294, USA
SOURCE: Journal of Membrane Biology (1994), 142(2), 171-9
CODEN: JMBBBO; ISSN: 0022-2631
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The goal of the present studies was to det. whether anion fluxes are involved in thrombin- and histamine-activated signal transduction pathways in human umbilical vein endothelial cells (HUVECs). 125Iodine (125I) efflux techniques were used to test the sensitivity of anion fluxes to increases in [Ca2+]i and activation of protein kinase C. HUVECs exhibited const. 125I efflux rates under basal conditions. **Administration** of **thrombin** or histamine stimulated an increase in 125I efflux rates which returned to control values after approx. 1-2 min. Since both agonists stimulate increases in [Ca2+]i, the authors tested the hypothesis that 125I efflux was sensitive to changes in [Ca2+]i. When HUVECs were exposed to ionomycin or thapsigargin, the 125I efflux rate increased and remained elevated for several minutes. In subsequent expts., HUVECs were incubated with the cell permeant Ca2+ chelator, 1,2-bis-(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid-AM, to buffer changes in [Ca2+]i. This **treatment** reduced both basal and thrombin-stimulated 125I efflux. However, when Ca2+ was removed from the efflux buffer and replaced with EGTA, peak thrombin-stimulated 125I efflux remained unchanged. This anion efflux was also sensitive to activation of protein kinase C since phorbol 12-myristate 13-acetate and phorbol

12,13-dibutyrate blunted thrombin-mediated increases in 125I efflux. Preincubation of HUVECs with protein kinase C inhibitor peptide [19-36] antagonized the phorbol ester-mediated decrease in thrombin-stimulated 125I efflux. It is suggested that 125I efflux in HUVECs represents a Ca2+-sensitive anion conductance and that intracellular Ca2+ release, but not extracellular Ca2+ influx, is sufficient to initiate channel activity.

L7 ANSWER 8 OF 27 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:103323 CAPLUS
DOCUMENT NUMBER: 120:103323
TITLE: Effects of NG-substituted arginines on coronary vascular function after endotoxin
AUTHOR(S): Winn, Mark J.; Vallet, Benoit; Asante, Nelson K.; Curtis, Scott E.; Cain, Stephen M.
CORPORATE SOURCE: Dep. Pharmacol., Univ. Alabama, Birmingham, AL, 35294, USA
SOURCE: Journal of Applied Physiology (1993), 75(1), 424-31
CODEN: JAPHEV; ISSN: 8750-7587
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors investigated the responses of canine coronary rings to endothelium-derived relaxing factor-nitric oxide- (EDRF-NO) dependent agonists and NO synthase (NOS) inhibitors 3 h after endotoxic shock was induced in dogs by lipopolysaccharide infusion (LPS; 2 mg/kg). EDRF-NO-dependent relaxation to thrombin [control max. response produced after **administration** of **thrombin** (Emax) was -85.2% of the constrictor response produced by the thromboxane analog U-46619], acetylcholine (control Emax -88.4%), or bradykinin (control Emax -80.5%) was not inhibited by LPS (Emax thrombin -75.9%; Emax acetylcholine -90.2%; Emax bradykinin -91.6%). The NOS inhibitor NG-monomethyl-L-arginine (L-NMMA) (10-6-3.times.10-4M) caused constriction of rings with endothelium (Emax 36.3%), an effect that was greater after LPS (Emax 59.2%). D-NMMA had no effect in control, but it increased tension after LPS (Emax 20.8%). Contrary to expectations, L- and D-NMMA relaxed endothelium-denuded rings (-30.4% L-NMMA; -45.1% D-NMMA). However, neither agent caused relaxation after in vivo LPS (10.2% L-NMMA; 8.9% D-NMMA). N.omega.-nitro-L-arginine-methylester (L-NAME) and nitro-L-arginine (10-6-3.times.10-4M) increased tension (Emax 82.3 and 73.1%, resp.) but only when endothelium was present, and the increases were no greater in LPS-**treated** groups than in controls (with LPS: Emax L-NAME 87.3%; Emax nitro-L-arginine 65.7%). Thus, NMMA may have influenced canine coronary vascular tone by a mechanism other than inhibition of LPS-induced NOS.

L7 ANSWER 9 OF 27 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:95183 CAPLUS
DOCUMENT NUMBER: 120:95183
TITLE: The effect of defibrotide on thromboembolism in the pulmonary vasculature of mice and rabbits and in the cerebral vasculature of rabbits
AUTHOR(S): Paul, W.; Gresele, P.; Momi, S.; Bianchi, G.; Page, C. P.
CORPORATE SOURCE: King's Coll., Univ. London, London, SW3 6LX, UK
SOURCE: British Journal of Pharmacology (1993), 110(4), 1565-71
CODEN: BJPCBM; ISSN: 0007-1188
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Administration of bovine thrombin (100 u kg-1) into the carotid artery of rabbits induces a sustained accumulation of 111Indium-labeled platelets within the cranial vasculature over the subsequent 3 h. Intracarotid (i.c.) administration of defibrotide (64 mg kg-1 bolus plus 64 mg kg-1 h-1 for 1 h) prior to i.c. thrombin (d100 u kg-1) significantly reduces the ability of thrombin to induce cranial thromboembolism in rabbits. I.v.

administration of **thrombin** (20 u kg-1) in rabbits induces a reversible accumulation of radiolabeled platelets into the thoracic circulation which is significantly reduced by i.v. administration of defibrotide (64 mg kg-1 bolus plus 64 mg kg-1 h-1 for 1 h) prior to i.v. thrombin. In contrast, platelet accumulation in response to ADP (ADP; 20 .mu.g kg-1, i.v.) or platelet activating factor (PAF; 50 ng kg-1, i.v.) is not significantly affected by this **treatment**. I.v. administration of the nitric oxide (NO)-synthase inhibitor NG-nitro-L-arginine Me ester (L-NAME; 10 mg kg-1) potentiates platelet accumulation induced by low dose thrombin (10 u kg-1, i.v.) within the pulmonary vasculature of rabbits. The potentiated response is significantly abrogated following pretreatment with defibrotide (64 mg kg-1 bolus plus 64 mg kg-1 h-1 for 1 h, i.v.). I.v. injection of human thrombin (1250 u kg-1) to mice induces death within the majority of animals which is significantly reduced by pretreatment with defibrotide (150-175 mg kg-1, i.v.). In contrast, death induced by i.v. collagen (1.25 mg kg-1) plus adrenaline (75 .mu.g kg-1) is not significantly affected by defibrotide pretreatment. The inhibitory effect of defibrotide in mice is abolished following concomitant **treatment** with the inhibitor of fibrinolysis, tranexamic acid (100 mg kg-1, i.v.), but is unaffected following **treatment** with the cyclo-oxygenase inhibitor, aspirin (300 mg kg-1, i.p.). The protective effect of defibrotide against thrombin-induced thromboembolism in the mouse is potentiated by recombinant tissue-plasminogen activator (rt-PA; 1 mg kg-1, i.v.) or unfractionated heparin (10 u kg-1, i.v.) administration. The results suggest that defibrotide may possess antithrombotic activity on thrombin-induced thromboembolism which, at least in the mouse, may be partially mediated via induction of the fibrinolytic pathway.

L7 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:535201 CAPLUS
DOCUMENT NUMBER: 127:171356
TITLE: Intra urinary bladder **administration** of **thrombin** in massive bleeding hemostasis
AUTHOR(S): Li, Zongliang; Yang, Huazhang; Cheng, Ying; Zhang, Honge
CORPORATE SOURCE: Guangdong Provincial People's Hospital, Canton, 510080, Peop. Rep. China
SOURCE: Guangdong Yixue (1997), 18(5), 345
CODEN: GUYIEG; ISSN: 1001-9448
PUBLISHER: Guangdongsheng Yixue Qingbao Yanjiuso
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Urinary bladder massive bleeding because of carcinoma in 3 cases and hemorrhagic cystitis in 1 case were **treated** by intra bladder **administration** of **thrombin** and showed satisfactory results. 4000 U of thrombin in 20-40 mL normal saline was retained in the bladder for 2 h b.i.d. for 3 days. 4 Patients obtained hemostasis within 1-5 days.

L7 ANSWER 26 OF 27 MEDLINE on STN
ACCESSION NUMBER: 91143626 MEDLINE
DOCUMENT NUMBER: 91143626 PubMed ID: 1705089
TITLE: A study on local **administration** of **thrombin** following transurethral resection of the prostate--clinical investigation with four-way balloon catheter.
AUTHOR: Izumi H; Kurokawa J; Yokoyama E
CORPORATE SOURCE: Department of Urology, Kitasato University School of Medicine.
SOURCE: HINYOKIKA KIYO. ACTA UROLOGICA JAPONICA, (1990 Nov) 36 (11) 1277-85. Ref: 22
Journal code: 0421145. ISSN: 0018-1994.
PUB. COUNTRY: Japan
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
General Review; (REVIEW)
(REVIEW OF REPORTED CASES)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199103
ENTRY DATE: Entered STN: 19910412
Last Updated on STN: 19960129
Entered Medline: 19910325

AB The effect of local **administration** of **thrombin** via a newly devised four-way balloon indwelling catheter was investigated on 89 patients who underwent transurethral resection of the prostate (TURP). The catheter was introduced into the bladder immediately after TURP, the balloon was inflated with sterile water and mild moist sponge traction was applied to seal the bladder neck for 15 minutes. At the same time, the thrombin solution, 5,000 U in 5 ml of saline, was then injected into the prostatic fossa via the newly added infusion channel to promote early hemostasis. The results were compared with those of 36 randomized control patients, who were **treated** with the conventional three-way balloon catheter of the same size. The results obtained with this new device were favorable, showing significantly less postoperative hemorrhage in the thrombin infusion group than in the control group. In 7 of 89 thrombin infused patients, serum FDP revealed mild elevation for 2 hours after TURP. In 2 of these 7 patients FDP was closely correlated with thrombin infusion. However, no adverse reactions were observed in any patient in the thrombin infusion group. In conclusion, our new device to administer locally the thrombin solution is effective and safe for management of bleeding after TURP.

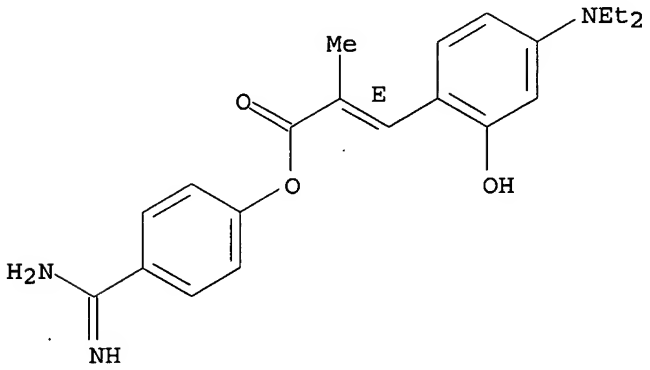
L8 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:528156 CAPLUS
DOCUMENT NUMBER: 127:218530
TITLE: In vivo photoactivation of caged-thrombin
AUTHOR(S): Arroyo, Jorge G.; Jones, Paul B.; Porter, Ned A.; Hatchell, Diane L.
CORPORATE SOURCE: Department Ophthalmology, Duke University, Durham, NC, 27710, USA
SOURCE: Thrombosis and Haemostasis (1997), 78(2), 791-793
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: Schattauer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aberrant ocular neovascularization is a major cause of blindness in the world. Abnormal blood vessels in the eye may produce corneal opacification, corneal transplant rejection, neovascular glaucoma, vitreous hemorrhage, traction retinal detachment, and subretinal scars from choroidal neovascular membranes. Light-induced clotting of blood within these abnormal vessels could provide a novel method for the ablation of deleterious neovascularization. Thrombin is a Ser proteinase that participates in the final stages of the coagulation cascade. P-amidinophenyl-(E)-4-diethylamino-2-hydroxy-.alpha.-methylcinnamate hydrochloridean inhibitor of thrombin, p-amidinophenyl-(E)-4-diethylamino-2-hydroxy-.alpha.-methylcinnamate hydrochloride, MeCINN, covalently attaches to the active site Ser hydroxyl, inhibiting or caging, the enzyme. Photolysis of the caged-thrombin in vitro causes a trans-cis isomerization of MeCINN which leads to regeneration of active enzyme and **cleaving** of fibrinogen into fibrin. Using a rabbit model of corneal neovascularization, it was found that light at 366 nm safely and effectively photoactivates i.v. caged-thrombin and produces localized thrombosis in vivo. These results suggest that intra-vascular photoactivation of caged-thrombin could be used to occlude abnormal blood vessels in the human eye.

IT **189570-73-8**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(photoactivation of caged-thrombin in eye blood vessel)

RN 189570-73-8 CAPLUS
CN 2-Propenoic acid, 3-[4-(diethylamino)-2-hydroxyphenyl]-2-methyl-, 4-(aminoiminomethyl)phenyl ester, (E)- (9CI) (CA INDEX NAME)

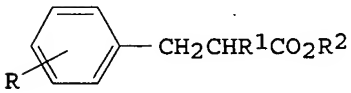
Double bond geometry as shown.



L10 ANSWER 12 OF 27 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1979:151829 CAPLUS
DOCUMENT NUMBER: 90:151829
TITLE: Amino- or guanidinophenylpropionic acid **esters**
PATENT ASSIGNEE(S): Torii and Co., Ltd., Japan
SOURCE: Belg., 46 pp.
CODEN: BEXXAL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BE 868414	A1	19781016	BE 1978-188813	19780623
JP 54009241	A2	19790124	JP 1977-75063	19770624
JP 61008818	B4	19860318		

PRIORITY APPLN. INFO.: JP 1977-75063 19770624
GI



I

AB **Esters** I [R = NH2, NHC(:NH)NH2; R1 = H, alkyl; R2 = Ph, alkyl-, (carboxyalkyl)-, alkoxy-, alkoxycarbonyl-, or halophenyl, naphthyl, halonaphthyl], which inhibited proteolytic enzymes, blood platelet aggregation, and hemolysis and showed usefulness in the treatment of Masugi nephritis, were prepd. from the resp. nitrocinnamic acids. 4-Nitrocinnamic acid was converted to the acid chloride which was treated with p-cresol to give the resp. ester; the ester was reduced by H over Pd/C to give I (R = 4-NH2, R1 = H, R2 = p-tolyl).

IT **39157-07-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and esterification of, by phenols)

RN 39157-07-8 CAPLUS
CN 2-Propenoyl chloride, 2-methyl-3-(4-nitrophenyl)- (9CI) (CA INDEX NAME)

L17 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:813875 CAPLUS
DOCUMENT NUMBER: 137:329436
TITLE: **Prodrugs** via acylation with **cinnamate**
INVENTOR(S): Gilbert, Carl W.; McGowan, Eleanor B.; Black, Kirby S.; Harper, Gregory T. P.
PATENT ASSIGNEE(S): Cryolife, Inc., USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002083067	A2	20021024	WO 2002-US11330	20020412
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002187992	A1	20021212	US 2002-66306	20020131

PRIORITY APPLN. INFO.:
US 2001-284304P P 20010417
US 2001-315782P P 20010828
US 2002-66306 A 20020131

AB A prodrug compn. contg. a **cinnamate** moiety and a biol. active mol. moiety which can be released by hydrolysis or activated by light is disclosed. The **cinnamate** moiety can have substituents of various electronically donating or electronically withdrawing groups to modify the **cinnamate** moiety's elec. properties as well as photo reactivities for the purpose of achieving a proper hydrolysis rate of the acyl bond between the biol. active mol. moiety and the cinnamic acid backbone. The biol. active mol. can be any biol. active agent or diagnostic, for example, a chemotherapeutic such as a paclitaxel, camptothecin, doxorubicin, amethopterin, etoposide, or fluconazole. The prodrug compn. can be modified to add a carrier moiety on the prodrug compn. for targeting or to facilitate uptake of the drug. The prodrug compns. can be activated with an energy source to release the drug at the desired site. Representative energy sources can be in the form of elec. force, ultrasound, light or radiation of a radioactive material which can be administered either externally or internally.

L30 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:100747 CAPLUS
DOCUMENT NUMBER: 130:144204
TITLE: Modified amino acids as carriers for enhanced delivery of active agents
INVENTOR(S): Leone-Bay, Andrea; Ho, Koc-kan; Sarubbi, Donald J.; Milstein, Sam J.
PATENT ASSIGNEE(S): Emisphere Technologies, Inc., USA
SOURCE: U.S., 27 pp., Cont.-in-part of U.S. Ser. No. 414,654. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 30
PATENT INFORMATION:

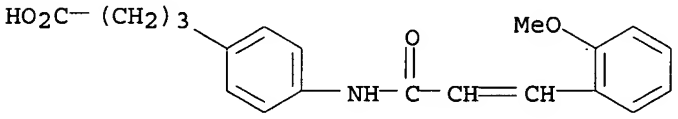
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5866536	A	19990202	US 1997-798033	19970206
US 5650386	A	19970722	US 1995-414654	19950331
CN 1190893	A	19980819	CN 1996-192998	19960401
US 6071510	A	20000606	US 1997-839094	19970423

PRIORITY APPLN. INFO.: US 1995-414654 A2 19950331

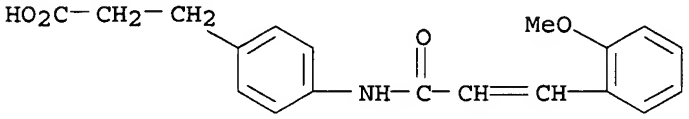
AB Carrier compds., compns., and dosage unit forms which are useful in the delivery of active agents are provided. The present invention provides compds. such as 10-salicyloylaminodecanoic acid (I) for delivery of at least one active agent, including peptides, mucopolysaccharides, carbohydrates, or lipids. I prepd. from 8-aminocaprylic acid and O-acetylsalicyloyl chloride was mixed with recombinant human growth hormone (rhGH) in a phosphate buffer soln. The compn. was orally administered to rats at I 200 mg/kg and rhGH 3 mg/kg and delivery was evaluated by an ELISA assay for rhGH; mean peak serum levels of rhGH was .apprx.60.92 ng/mL as compared to <0.1 ng/mL for control group received a compn. without I.

IT **177653-52-0 177653-65-5 183990-75-2**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modified amino acids as carriers for enhanced delivery of active agents)

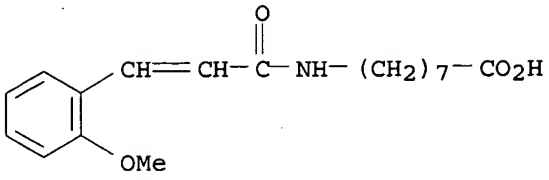
RN 177653-52-0 CAPLUS
CN Benzenebutanoic acid, 4-[[3-(2-methoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



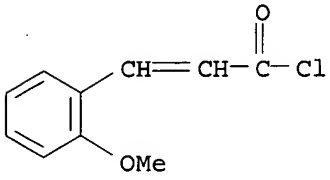
RN 177653-65-5 CAPLUS
CN Benzenepropanoic acid, 4-[[3-(2-methoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



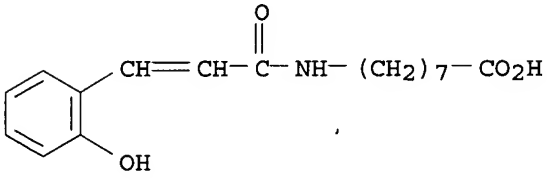
RN 183990-75-2 CAPLUS
CN Octanoic acid, 8-[[3-(2-methoxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



IT **15851-91-9**, 2-Methoxycinnamoyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of modified amino acids as carriers for enhanced delivery of active agents)
RN 15851-91-9 CAPLUS
CN 2-Propenoyl chloride, 3-(2-methoxyphenyl)- (9CI) (CA INDEX NAME)



IT **183990-49-0P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of modified amino acids as carriers for enhanced delivery of active agents)
RN 183990-49-0 CAPLUS
CN Octanoic acid, 8-[[3-(2-hydroxyphenyl)-1-oxo-2-propenyl]amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1937:41896 CAPLUS
DOCUMENT NUMBER: 31:41896
ORIGINAL REFERENCE NO.: 31:5865g-i,5866a
TITLE: Unsaturated group in therapeutic substances
AUTHOR(S): Ehrhart, Gustav
SOURCE: Med. u. Chem. Abhandl. med.-chem. Forschungsstatten I. G. Farbenind. (1936), 3, 366-74
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB The adverse effect of introducing or retaining an unsatd. group in a drug is pictured by contrasting the therapeutic effect of hydroquinine and arecoline with quinine and the allyl substitution products of arecoline. The opposite action is demonstrated by the transformation of the blood-pressure-raising ephedrine into the allyl and **cinnamyl derivs**. which lower the blood pressure, act as vasodilators and have a cocaine-like anesthetic action. After the successful use of the guanidines Synthalin and Synthalin B in diabetes, the plant alkaloid, galegine (I) isoamylenylguanidine has been synthesized by converting the catalytic reduction product of methylbutinol, methylbutenol, into isoamylenyl bromide and treating the corresponding amine with (MeS.C(:NH)NH2)2.H2SO4. I gave hypoglucemic effects and proved toxic. The introduction of the unsatd. group into **drugs** has proved particularly useful in enhancing the hypnotic properties of the barbiturates, of which more than 100 have been prepd. and tested. Similar acetylenic compds., isopropylpropargyl and isopropylisopropenylpropargyl barbituric acids, have also been prepd. and tested but not promoted commercially. Analogous increase in properties has been noted in the diethylpropylacetamide series, novanol, ethyldiallylacetamide and triallylacetamide.

=> s cinnamoyl
L33 4266 CINNAMOYL

=> s hydroxycinnamoyl
L34 481 HYDROXYCINNAMOYL

=> s l34 and drugs
L35 2 L34 AND DRUGS

=> d l35 1-2 ibib abs

L35 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:218121 CAPLUS
TITLE: Milkweed cardenolide inhibition of Na+, K+-ATPase.
AUTHOR(S): Dougherty, Michelle M.; Abbott, Alan J.; Martin, Ronald A.
CORPORATE SOURCE: Department Chemistry, Louisiana State University Shreveport, Shreveport, LA, 71115, USA
SOURCE: Book of Abstracts, 211th ACS National Meeting, New Orleans, LA, March 24-28 (1996), CHED-273. American Chemical Society: Washington, D. C.
CODEN: 62PIAJ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Cardiac glycosides are **drugs** used in the treatment of heart failures. They belong to the cardenolide family of compds. and inhibit the enzyme Na+, K+-ATPase for their physiol. response. In this study, a new cardenolide, 6'-0-(E-4-**hydroxycinnamoyl**) desglucouzarin, was tested for its ability to behave as a cardiac glycoside. The cardenolide was isolated from an Asclepias milkweed, and its inhibitory potency will be compared to that of a known cardiac glycoside, ouabain.

L35 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:218121 CAPLUS
TITLE: Milkweed cardenolide inhibition of Na+, K+-ATPase.
AUTHOR(S): Dougherty, Michelle M.; Abbott, Alan J.; Martin, Ronald A.
CORPORATE SOURCE: Department Chemistry, Louisiana State University Shreveport, Shreveport, LA, 71115, USA
SOURCE: Book of Abstracts, 211th ACS National Meeting, New Orleans, LA, March 24-28 (1996), CHED-273. American Chemical Society: Washington, D. C.
CODEN: 62PIAJ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB Cardiac glycosides are **drugs** used in the treatment of heart failures. They belong to the cardenolide family of compds. and inhibit the enzyme Na+, K+-ATPase for their physiol. response. In this study, a new cardenolide, 6'-O-(E-4-**hydroxycinnamoyl**) desglucouzarin, was tested for its ability to behave as a cardiac glycoside. The cardenolide was isolated from an Asclepias milkweed, and its inhibitory potency will be compared to that of a known cardiac glycoside, ouabain.

L35 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1966:61396 CAPLUS
DOCUMENT NUMBER: 64:61396
ORIGINAL REFERENCE NO.: 64:11536f-h,11537a-b
TITLE: Specificity of the nitrosonaphthol reaction in the determination of urinary 5-hydroxyindoleacetic acid
AUTHOR(S): Mustala, Olli O.
CORPORATE SOURCE: Dept. Pharmacol., Univ. Helsinki
SOURCE: Ann. Med. Exptl. Biol. Fenniae (Helsinki), Suppl. (1965), 43(8), 48 pp.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Substances were tested for color reaction with nitrosonaphthol (I) by adding to 1 ml. of a 10 mM soln. of the unknown, 1 ml. of 0.1% I soln. in 96% EtOH and 1 ml. of a HNO2 reagent composed of 1 ml. of 5% NaNO2 in 10 ml. of 2N H2SO4. The mixt. was heated at 37.degree. for 5 min., then washed twice with EtOAc. Compds. were also examd. for color reaction with HNO2 alone by the above method. Substances were observed further by adding I and (or) HNO2 reagent to the unknown on filter paper. Color with HNO2 only developed with apomorphine, diphenylamine, guaiacol, hexylresorcinol, indole, indoleacetic acid, 1-naphthol, 2-naphthol, thymol, Na 2-naphthol-6-sulfonate, and pyrogallolcarboxylic acid. No I reaction was noted in the 21 aliphatic, 46 nonaromatic, or 96 aromatic compds. examd. Of 113 substances contg. a phenolic OH, 38 produced a pos. I reaction. The color-forming compd. must contain a phenolic OH group, and both the ortho and at least 1 of the meta positions to the OH group must be free. Color formation was possible only where an aliphatic, alicyclic, or aromatic compd. was joined to the meta- and (or) para-position, directly or by means of an O or N atom. The substituent joined to the benzene ring must, at least in 1 position, be aliphatic, aromatic, or alicyclic and join the ring either directly or through an O or N bond. The urine from healthy humans showed 13 I-pos. substances, of which 4 were definitely identified as phenolic acids. Other color-pos. substances were found during pregnancy and in patients with various diseases. **Drugs** known or suspected of forming I-pos. metabolites were administered to normal humans in 2-4 doses over 24 hrs. Urine was collected for 4 hrs. pretreatment and for 36 hrs. after the 1st dose. The urine was examd. untreated and hydrolyzed with HCl. Among the 62 **drugs** examd., 12 of which were known to be I-pos., 22 I-pos. metabolites were formed, 9 of which were excreted as original **drugs** and 13 as products of metabolism. I-pos. metabolites not described before were formed from glyceryl guaiacolate, methocarbamol, methoxyphenamine, and sulfobromophthalein. Hydroxylation in the benzene ring occurred in humans, esp. with **drugs** having a MeO group joined to the benzene ring. To prevent false-pos. 5-hydroxyindoleacetic acid (II) reactions, the method of Udenfriend, et al. (CA 50, 1970e), was improved by including the following: diln. of the urine for better recovery of II, higher concn. of the HNO2 reagent for elimination of false-neg. results, higher temp. for color reaction, development of the color at room temp. for 2 hrs., and measurement of color at 2 wavelengths. By this new method the excretion of II for healthy adults averaged 4.55 mg./24 hrs. The value is lower than those reported by the Udenfriend method, because the addnl. steps eliminate interference by alimentary phenolic acids. The recovery of II was 80%.

=> d his

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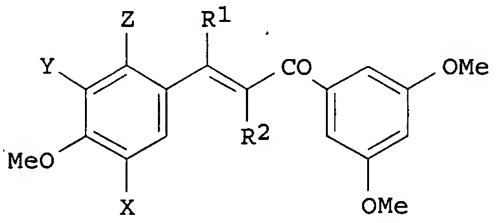
L1 STRUCTURE UPLOADED
L2 14 S L1 SSS SAM

L35 ANSWER 16 OF 47 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:730676 CAPLUS
DOCUMENT NUMBER: 135:272794
TITLE: Preparation of substituted chalcones for pharmaceutical use in the treatment of cancer
INVENTOR(S): Potter, Gerard Andrew; Butler, Paul Crispin; Wanogho, Elugba
PATENT ASSIGNEE(S): Cancer Research Ventures Limited, UK
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072680	A1	20011004	WO 2001-GB1341	20010326
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1284952	A1	20030226	EP 2001-914064	20010326
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003100538	A1	20030529	US 2002-239757	20020926

PRIORITY APPLN. INFO.: GB 2000-7401 A 20000327
WO 2001-GB1341 W 20010326

OTHER SOURCE(S): MARPAT 135:272794
GI



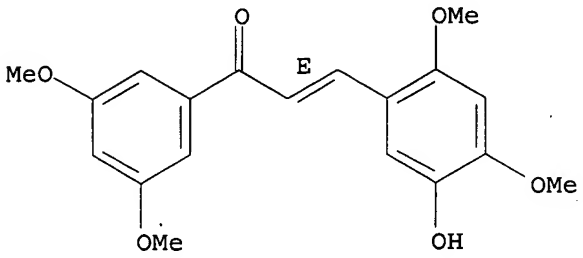
I

AB Chalcones, such as I [R1, R2 = H, alkyl, fluoroalkyl; X = H, OH, OSO3H, OPO3H2, acyloxy; Y = H, alkyl; Z = H, OMe], were prepd. for use in the diagnosis and treatment of proliferative conditions, such as cancer, and inflammatory conditions. Thus, chalcone I (R1 = R2 = X = Y = Z = H) was prepd. in 68% yield by reaction of MeO-4-C6H4CHO and 3,5-Me2C6H3COMe in MeOH using a 50% aq. soln of NaOH. The prepd. chalcones were tested for antitumor activity against breast MCF-7, colon HCT-116 and lung A-549 cancer cell lines.

IT **363608-87-1P 363608-88-2P 363608-89-3P**
363619-02-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted chalcones for pharmaceutical for therapeutic use in the treatment of cancer, inflammation, and proliferative conditions)

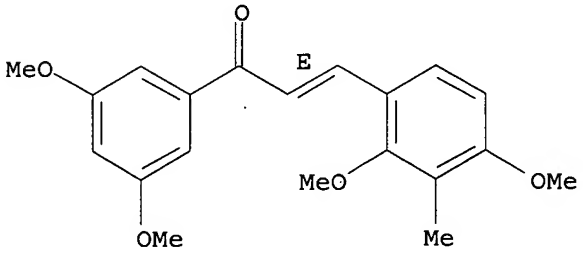
RN 363608-87-1 CAPLUS
CN 2-Propen-1-one, 1-(3,5-dimethoxyphenyl)-3-(5-hydroxy-2,4-dimethoxyphenyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



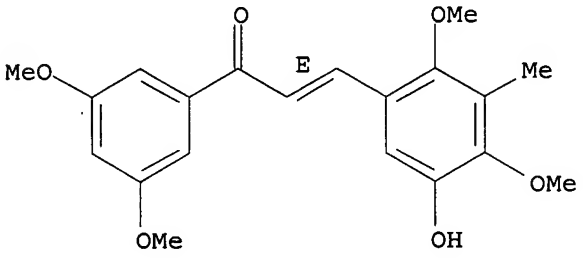
RN 363608-88-2 CAPLUS
CN 2-Propen-1-one, 3-(2,4-dimethoxy-3-methylphenyl)-1-(3,5-dimethoxyphenyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



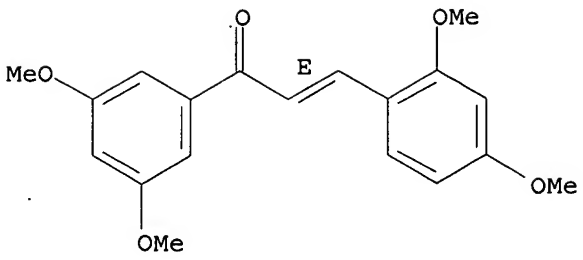
RN 363608-89-3 CAPLUS
CN 2-Propen-1-one, 1-(3,5-dimethoxyphenyl)-3-(5-hydroxy-2,4-dimethoxy-3-methylphenyl)-, (2E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 363619-02-7 CAPLUS
CN 2-Propen-1-one, 3-(2,4-dimethoxyphenyl)-1-(3,5-dimethoxyphenyl)-, (2E)-(9CI) (CA INDEX NAME)

Double bond geometry as shown.



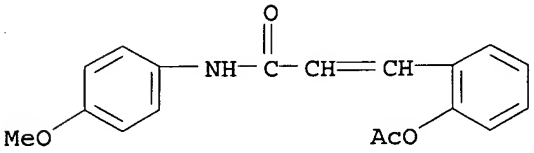
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 38 OF 47 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:288883 CAPLUS
DOCUMENT NUMBER: 125:25637
TITLE: Chemical feasibility studies of a potential coumarin-based **prodrug** system
AUTHOR(S): Wang, Binghe; Zhang, Huijuan; Wang, Wei
CORPORATE SOURCE: College Pharmacy, Univ. Oklahoma Health Sciences Center, Oklahoma City, OK, 73190, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1996), 6(8), 945-950
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

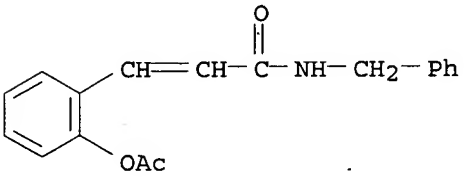
AB By using model amines, several amides of coumarinic acid with the phenolic hydroxyl group protected as an ester were prepd. These model amides underwent a facile (t1/2 1.5-31 min) lactonization to release the original amine compds. upon esterase catalyzed hydrolysis of the phenolic ester. Such a system can be used for the prepn. of esterase-sensitive **prodrugs** of amine-contg. compds. or peptides.

IT **177708-37-1P 177708-38-2P 177708-39-3P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and esterase sensitivity of potential coumarin-based **prodrug**)

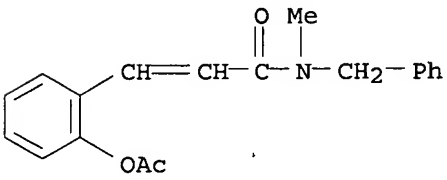
RN 177708-37-1 CAPLUS
CN 2-Propenamide, 3-[2-(acetyloxy)phenyl]-N-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



RN 177708-38-2 CAPLUS
CN 2-Propenamide, 3-[2-(acetyloxy)phenyl]-N-(phenylmethyl)- (9CI) (CA INDEX NAME)



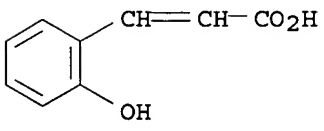
RN 177708-39-3 CAPLUS
CN 2-Propenamide, 3-[2-(acetyloxy)phenyl]-N-methyl-N-(phenylmethyl)- (9CI) (CA INDEX NAME)



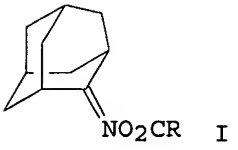
L35 ANSWER 45 OF 47 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1990:611106 CAPLUS
DOCUMENT NUMBER: 113:211106
TITLE: The lactonization of 2'-hydroxyhydrocinnamic acid amides: a potential **prodrug** for amines
AUTHOR(S): Amsberry, Kent L.; Borchardt, Ronald T.
CORPORATE SOURCE: Dep. Pharm. Chem., Univ. Kansas, Lawrence, KS, 66045, USA
SOURCE: Journal of Organic Chemistry (1990), 55(23), 5867-77
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 113:211106

AB The lactonization of 2 hydroxy amides - 4-methoxyaniline 3-(2'-hydroxyphenyl)-3,3-dimethylpropionic acid amide (I) and 4-methoxyaniline 3-(2'-hydroxy-4',6'-dimethylphenyl)-3,3-dimethylpropionic acid amide (II) - was studied over a pH range of 1-8. Due to the slowness of its reaction, a third hydroxy amide - 4-methoxyaniline 3-(2'-hydroxyphenyl)propionic acid amide (III) - was investigated only at pH values of 7.5 and 10. The lactonization of I and II, which was subject to general catalysis by buffer components, was obsd. to be catalyzed concurrently but not concertedly by both the acidic and basic forms of the buffer. The buffer-independent pH rate profiles for the lactonization of I and II obeyed the equation k0 - kH+[H3O+] + kH2O + kOH-[OH-], indicating that the reaction is also subject to specific catalysis by hydronium and hydroxide ions. A Broensted anal. of the rate consts. for buffer catalysis gave .alpha. and .beta. values of 0.30 .+-. 0.02 and 0.54 .+-. 0.04, resp., for II. The rate consts. for the accelerated lactonization of III at 50, 70, and 90.degree. and pH 10 were used to calc. values of 14.7 .+-. 0.8 kcal/mol and -8.5 .+-. 2.3 eu for the activation parameters, .DELTA.H.thermod. and .DELTA.S.thermod., resp. Comparison of the obsd. rates of lactonization at pH 7.5 and 30.degree. for the three hydroxy amides allowed an est. of the extent of rate enhancement provided by addn. of a partial or total tri-Me lock for the hydroxy amide lactonization reaction under near physiol. conditions. The order of reactivity of the three hydroxy amides was II .mchgt. I > III with rate enhancement factors of 2.5 .times. 104, 44, and 1, resp. II, which exhibited a half-life of 65 s at pH 7.5, was chosen for further development as an amine **prodrug**.

IT **583-17-5**
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydrogenation of)
RN 583-17-5 CAPLUS
CN 2-Propenoic acid, 3-(2-hydroxyphenyl)- (9CI) (CA INDEX NAME)



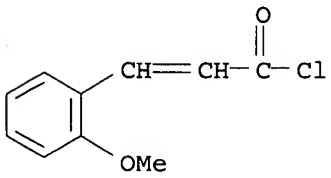
L35 ANSWER 46 OF 47 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1986:583581 CAPLUS
DOCUMENT NUMBER: 105:183581
TITLE: Synthesis and biological activity of 2-adamantanone oxime ester derivatives
AUTHOR(S): St. Georgiev, Vassil; Radov, Lesley A.; Kinsolving, C. Richard; Griffith, Ronald C.; Zazulak, Walter I.; Kamp, Dietgard K.; Trusso, Laura A.; Mack, Robert A.
CORPORATE SOURCE: Dep. Org. Chem., Pennwalt Corp., Rochester, NY, 14623, USA
SOURCE: European Journal of Medicinal Chemistry (1986), 21(4), 315-19
CODEN: EJMCA5; ISSN: 0223-5234
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 105:183581
GI



I

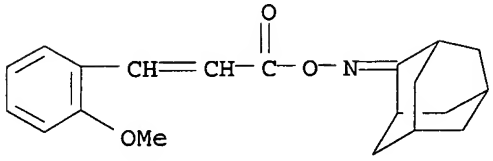
AB A series of I (R = Me, substituted Ph, phenylalkyl or phenylalkenyl) were prepd. by reaction of 2-adamantanone oxime [4500-12-3] with appropriate acyl chlorides in the presence of NaH. I (R = PhCH2) (II) [94719-71-8] was the most potent compd. when tested for anti-inflammatory activity in the carrageenin-induced rat paw edema assay. Most compds. were less potent than cloximate [4-ClC6H4CMe:NOCH2CO2CH2CH2NMe2) [58832-67-0] showing the importance of the haloacetophenone moiety. The activity of I was attributed to the intact mol. rather than a **prodrug** as shown by testing carboxylic acid and oxime hydrolysis products of I. The conformational anal. of II and cloximate showed similarities which contribute to activity. A nearly exact match of these 2 mols. in the oxime region was obsd. with the adamantane ring system filling the space between the Me group and the Ph ring of the lipophilic head group of cloximate.

IT **15851-91-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation by, of adamantanone oxime)
RN 15851-91-9 CAPLUS
CN 2-Propenoyl chloride, 3-(2-methoxyphenyl)- (9CI) (CA INDEX NAME)



IT **94719-80-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and inflammation inhibiting activity of)
RN 94719-80-9 CAPLUS

CN Tricyclo[3.3.1.13,7]decanone, O-[3-(2-methoxyphenyl)-1-oxo-2-propenyl]oxime (9CI) (CA INDEX NAME)



L39 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:163041 CAPLUS
DOCUMENT NUMBER: 132:170879
TITLE: **Bioactive** agents and analogs derived from Curcuma zedoaria for topical use in dentistry
INVENTOR(S): Kozlowski Junior, Vitoldo Antonio; Schimidt, Dionezine de Fatima Navarro; Sandrini, Julio Cezar
PATENT ASSIGNEE(S): Brazil
SOURCE: Braz. Pedido PI, 13 pp.
CODEN: BPXXDX
DOCUMENT TYPE: Patent
LANGUAGE: Portuguese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BR 9704328	A	19990518	BR 1997-4328	19971015

PRIORITY APPLN. INFO.: BR 1997-4328 19971015

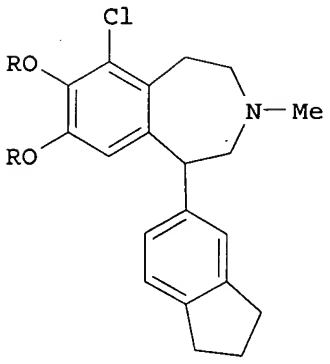
AB **Bioactive** principles for use in oral medicine are disclosed which are derived from medicinal plants in the genus Curcuma and can be used as topical agents in the oral cavity as coadjuvants in control of bacterial plaque and inflammatory responses by creation of forms devoid of toxicity. Compds. include derivs. of germacrane, elemane, cadinane, eudesmane, and guaiane such as curcumin, bis[4-**hydroxycinnamoyl**]methane, and 4-**hydroxycinnamoyl** feruloyl methane. The compds. can be administered as solns. in the form of mouthwashes or gargles.

L41 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:511303 CAPLUS
DOCUMENT NUMBER: 139:85244
TITLE: Preparation of benzazepines for therapeutic use as dopamine D1 receptor agonist **prodrugs**
INVENTOR(S): Tilbrook, Gary Stuart
PATENT ASSIGNEE(S): Shire Pharmaceutical Development Ltd., UK
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003053936	A1	20030703	WO 2002-GB5809	20021219

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2001-30576 A 20011220
GI



I

AB 2,3,4,5-Tetrahydro-1H-3-benzazepines, such as I [R = acyl, such as benzoyl, thiophene-2(or 3)-carbonyl, 3-phenylacryloyl, phenylacetyl, alkanoyl], were prepd. for pharmaceutical use as dopamine D1 receptor agonist **prodrugs**. Thus, the hydrochloride salt of benzazepine deriv. I (R = COPh) was prepd. by O-acylation of the corresponding diol I (R = H) with benzoyl chloride using TFA.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:202516 CAPLUS
DOCUMENT NUMBER: 138:210281
TITLE: Derivatives of pseudo-peptides, their preparation and

their biological uses
INVENTOR(S): Zimmer, Robert H.
PATENT ASSIGNEE(S): Fr.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003020321	A2	20030313	WO 2002-IB3605	20020906

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003060413	A1	20030327	US 2002-237254	20020906

PRIORITY APPLN. INFO.: US 2001-317736P P 20010906

AB Disclosed herein is a prodrug for use in the treatment of physiol. conditions comprising a carrier moiety selected from the consisting essentially of **cinnamoyl**, benzoyl, phenylacetyl, 3,4-methylenedioxycinnamoyl and 3,4,5-trimethoxycinnamoyl, wherein the carrier moiety is chem. linked to a therapeutic pseudo-polypeptide of the formula aan, where aa is a chem. modified amino acid, or a chem. or structural variation thereof, where n is an integer from 2 to 40, and wherein the pseudo-polypeptide is poorly absorbed orally. In an alternative variation, the prodrug of the present invention further comprises a non-therapeutic linker species linking the pseudo-polypeptide to the carrier moiety. Preferably, the linker species is an amino acid. Thus, the prodrug of the present invention can be viewed as a three-component entity: the first, therapeutically active component is the pseudo-polypeptide; the second is the linker species, possibly an addnl., non-therapeutic amino acid; and the third is the carrier moiety. Also disclosed are methods for the enhancement of the bioavailability of orally administered polypeptide substances.

L41 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:555380 CAPLUS
DOCUMENT NUMBER: 137:114533
TITLE: Compositions and methods for enhanced pharmacological activity through oral and parenteral administration of compositions comprising polypeptide drug substances and other poorly absorbed active ingredients
INVENTOR(S): Zimmer, Robert A.
PATENT ASSIGNEE(S): Fr.
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002056916	A2	20020725	WO 2002-IB133	20020117

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002132777 A1 20020919 US 2002-50903 20020116
PRIORITY APPLN. INFO.: US 2001-262337P P 20010117
US 2001-287872P P 20010501
US 2001-287886P P 20010501
US 2001-332636P P 20011106

AB Disclosed herein are novel pharmaceutical agents and compns., as well as novel methods, to enhance the absorption of polypeptide drug substances that normally display little if any absorbability if administered orally. Also disclosed are novel compns. and methods to significantly enhance the bioavailability and pharmacol. efficacy of polypeptide drug substances whether administered orally or parenterally. Analgesic effects from administration of CY5M, a **cinnamoyl**-Met-enkephalin prodrug were studied in a hot plate test with rats both when administered orally and when administered parenterally. The results demonstrated a strong, long-lasting analgesia.

L41 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:730744 CAPLUS
DOCUMENT NUMBER: 135:288790
TITLE: Pyrrolopyrimidines as tyrosine kinase inhibitors
INVENTOR(S): Hirst, Gavin C.; Calderwood, David; Munschauer, Rainer; Arnold, Lee D.; Johnston, David N.; Rafferty, Paul
PATENT ASSIGNEE(S): Basf Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 453 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072751	A1	20011004	WO 2000-US8593	20000329

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2000-US8593 20000329
OTHER SOURCE(S): MARPAT 135:288790
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Chem. compds. having structural formula I and physiol. acceptable salts and metabolites thereof, are inhibitors of serine/threonine and tyrosine kinase activity. Several of the kinases, whose activity is inhibited by these chem. compds., are involved in immunol., hyperproliferative, or

angiogenic processes. Thus, these chem. compds. can ameliorate disease states where angiogenesis or endothelial cell hyperproliferation is a factor. These compds. can be used to treat cancer and hyperproliferative disorders, rheumatoid arthritis, disorders of the immune system, transplant rejections and inflammatory disorders. All exemplified compds. significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at .ltoreq.50 .mu.M, and some significantly inhibited cdc2 at .ltoreq.50 .mu.M. In I, ring A is a six membered arom. ring or a five or six membered heteroarom. ring which is optionally substituted. L is -O-, -S-, -S(O)-, -S(O)2-, -N(R)-, -N[C(O)OR]-, -N[C(O)R]-, -N(SO2R)-, -CH2O-; -CH2S-, -CH2N(R)-, -C(NR)-; -CH2N[C(O)R]-, -CH2N[C(O)OR]-, -CH2N(SO2R)-, -CH(NHR)-, -CH[NHC(O)R]-, -CH(NHSO2R)-, -CH[NHC(O)OR]-, -CH[OC(O)R]-, -CH[OC(O)NHR]-, -CH:CH-; -C(:NOR)-, -C(O)-, -CH(OR)-, -C(O)N(R)-, -N(R)C(O)-, -N(R)S(O)-, -N(R)S(O)2-, -OC(O)N(R)-, -N(R)C(O)N(R)-, -NRC(O)O-, -S(O)N(R)-, -S(O)2N(R)-, -N[C(O)R]S(O)-, -N[C(O)R]S(O)2-, -N(R)S(O)N(R)-, -N(R)S(O)2N(R)-, -C(O)N(R)C(O)-, -S(O)N(R)C(O)-, -S(O)2N(R)C(O)-, -OS(O)N(R)-, -OS(O)2N(R)-, -N(R)S(O)O-, -N(R)S(O)2O-, -N(R)S(O)C(O)-, -N(R)S(O)2C(O)-, -SON[C(O)R]-, -SO2N[C(O)R]-, -N(R)SON(R)-, -N(R)SO2N(R)-, -C(O)O-, -N(R)P(OR')O-, -N(R)P(OR')-, -N(R)P(O)(OR')O-, -N(R)P(O)(OR')-, -N[C(O)R]P(OR')O-, -N[C(O)R]P(OR')-, -N[C(O)R]P(O)(OR')O-, -N[C(O)R]P(OR')-, -CH(R)S(O)-, or -CH(R)S(O)2-. L is also -CH(R)N[C(O)OR]-, -CH(R)N[C(O)R]-, -CH(R)N(SO2R), -CH(R)O-, -CH(R)S-, -CH(R)N(R)-, -CH(R)N[C(O)R]-, - CH(R)N[C(O)OR]-, -CH(R)N(SO2R)-, -CH(R)C(:NOR)-, -CH(R)C(O)-, -CH(R)CH(OR)-, -CH(R)C(O)N(R)-, -CH(R)N(R)C(O)-, -CH(R)N(R)S(O)-, -CH(R)N(R)S(O)2-, -CH(R)OC(O)N(R)-, -CH(R)N(R)C(O)N(R)-, -CH(R)N(R)C(O)O-, -CH(R)S(O)N(R)-, -CH(R)S(O)2N(R)-, -CH(R)N[C(O)R]S(O)-, -CH(R)N[C(O)R]S(O)2-, -CH(R)N(R)S(O)N(R)-, -CH(R)N(R)S(O)2N(R)-, -CH(R)C(O)N(R)C(O)-, -CH(R)S(O)N(R)C(O)-, -CH(R)S(O)2N(R)C(O)-, -CH(R)OS(O)N(R)-, -CH(R)OS(O)2N(R)-, -CH(R)N(R)S(O)O-, -CH(R)N(R)S(O)2O-, -CH(R)N(R)S(O)C(O)-, -CH(R)N(R)S(O)2C(O)-, -CH(R)SON[C(O)R]-, -CH(R)S(O)2N[C(O)R]-, -CH(R)N(R)SON(R)-, -CH(R)N(R)S(O)2N(R)-; -CH(R)C(O)O-, -CH(R)N(R)P(OR')O-, -CH(R)N(R)P(OR')-, -CH(R)N(R)P(O)(OR')O-, -CH(R)N(R)P(O)(OR')-, -CH(R)N[C(O)R]P(OR')O-, -CH(R)N[C(O)R]P(OR')-, -CH(R)N[C(O)R]P(O)(OR')O- or -CH(R)N[C(O)R]P(OR')-. In L, each R and R' is, independently, -H, acyl, substituted or unsubstituted aliph., arom., arylalkyl, heteroarom., cycloalkyl or arylalkyl; or L is -RbN(R)S(O)2-, -RbN(R)P(O)-, or -RbN(R)P(O)O-, wherein Rb is an alkylene group which when taken together with the sulfonamide, phosphinamide, or phosphonamide group to which it is bound forms a five or six membered ring fused to ring A; or L is II (X = O or nil; Y = O or nil) or III (Y = O, nil) wherein R85 taken together with the phosphinamide, or phosphonamide is a 5-, 6-, or 7-membered, arom., heteroarom. or heterocycloalkyl ring system. G is a direct bond, -(CH2)j- (j = 1-6), C2-C6-alkenylene, C3-C8-cycloalkylene or C1-C6-oxaalkylene group. R1 is substituted or optionally substituted aliph., cycloalkyl, bicycloalkyl, cycloalkenyl, arom., heteroarom., heteroaralkyl, heterocycloalkyl, heterobicycloalkyl, alkylamido, arylamido, -S(O)2-alkyl, -S(O)2-cycloalkyl, -C(O)alkyl, or -B-E, wherein B is substituted or unsubstituted cycloalkyl, heterocycloalkyl, arom., heteroarom., alkylene, aminoalkyl, alkylenecarbonyl, or aminoalkylcarbonyl and E is substituted or unsubstituted azacycloalkyl, azacycloalkylcarbonyl, azacycloalkylsulfonyl, azacycloalkylalkyl, heteroaryl, heteroarylcarbonyl, heteroarylsulfonyl, heteroaralkyl, alkyl sulfonamido, aryl sulfonamido, bicycloalkyl, ureido, thioureido or aryl. R2 is -H or substituted or unsubstituted aliph., cycloalkyl, halogen, -OH, cyano, arom., heteroarom., heterocycloalkyl, aralkyl, heteroaralkyl, -(CH2)0-3NR4R5, or -(CH2)0-3C(O)NR4R5. R3 is substituted or unsubstituted aliph., alkenyl, cycloalkyl, arom., heteroarom., or heterocycloalkyl with provisos. R4, R5 and the N atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocycloalkyl, heterobicycloalkyl or heteroarom.; or R4 and R5 are each, independently, -H, azabicycloalkyl, heterocycloalkyl, substituted or unsubstituted alkyl or Y-Z; Y is -C(O)-, -(CH2)p-, -S(O)2-, -C(O)O-, -SO2NH-, -CONH-, -(CH2)pO-, -(CH2)pNH-, -(CH2)pS-, -(CH2)pS(O)-, and -(CH2)pS(O)2-; p = 0-6; and Z is -H, or substituted or unsubstituted

alkyl, amino, aryl, heteroaryl or heterocycloalkyl. 546 Example prepns. are included. For example, addn. of piperidine to 4-[4-amino-5-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl]cyclohexanone in DCE and AcOH, followed by treatment with Na[(AcO)3BH], workup and chromatog., gave cis- and trans-IV.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

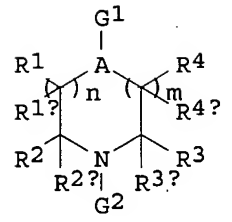
L41 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2001:78383 CAPLUS
DOCUMENT NUMBER: 134:163059
TITLE: Substituted piperazinone derivatives and other oxoazaheterocyclyl compounds useful as factor Xa/IIa inhibitors
INVENTOR(S): Ewing, William R.; Becker, Michael R.; Choi-Sledeski, Yong Mi; Pauls, Heinz W.; He, Wei; Condon, Stephen M.; Davis, Roderick S.; Hanney, Barbara A.; Spada, Alfred P.; Burns, Christopher J.; Jiang, John Z.; Li, Aiwen; Myers, Michael R.; Lau, Wan F.; Poli, Gregory B.
PATENT ASSIGNEE(S): Aventis Pharmaceuticals Products Inc., USA
SOURCE: PCT Int. Appl., 460 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007436	A2	20010201	WO 2000-IB1156	20000726
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000013179	A	20020402	BR 2000-13179	20000726
EP 1208097	A2	20020529	EP 2000-951781	20000726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003508353	T2	20030304	JP 2001-512520	20000726
EE 200200045	A	20030616	EE 2002-45	20000726
NO 2002000214	A	20020402	NO 2002-214	20020115
BG 106340	A	20021031	BG 2002-106340	20020122

PRIORITY APPLN. INFO.: US 1999-363196 A 19990728
WO 2000-IB1156 W 20000726

OTHER SOURCE(S): MARPAT 134:163059
GI



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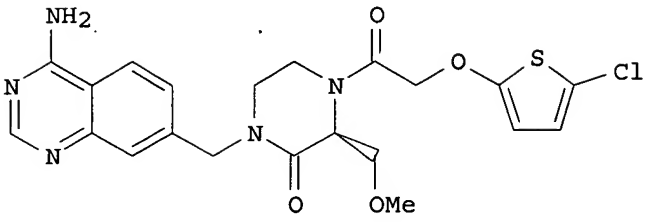

II

AB The invention is directed to piperazinones I and their pharmaceutically acceptable salts, **prodrugs**, N-oxides, hydrates, and solvates [wherein A = CH or N; G1 and G2 = L1Cy1 or L2Cy2; Cy1 and Cy2 = (un)substituted aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl, etc.; L1 = null, O, S, SO, SO2, or (un)substituted sulfamoyl, methylene, (alkyl)keto(alkyl), carbamoyl, etc.; L2 = null or linking group; R1, R1a, R2, R2a, R3, R3a, R4, R4a = independently H, carboxy, alkoxycarbonyl, alkyl, (hetero)aryl, aralkyl, heteroarylalkyl, etc.; m and n = independently 0-2]. The compds. inhibit factor Xa (no data) and factor IIa, and thereby the prodn. of thrombin, and are thus useful as anticoagulants in the treatment of a wide variety of conditions. The invention is also directed to pharmaceutical compns., synthetic intermediates, and a method of inhibiting factor Xa. Examples include the synthesis of approx. 1600 invention compds. and several hundred intermediates. For instance, condensation of 5-chloro-2-thienyloxyacetic acid with the corresponding N-benzyloxycarbonyl-protected piperazinone deriv. (prepns. given), using DIPEA and TBTU in DMF, gave II.

L41 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:31473 CAPLUS
DOCUMENT NUMBER: 134:100864
TITLE: Indazole compounds and pharmaceutical compositions for inhibiting protein kinases, and methods for their use
INVENTOR(S): Kania, Robert Steven; Bender, Steven Lee; Borchardt, Allen J.; Braganza, John F.; Cripps, Stephan James; Hua, Ye; Johnson, Michael David; Johnson, Theodore Otto, Jr.; Luu, Hiep The; Palmer, Cynthia Louise; Reich, Siegfried Heinz; Tempczyk-russell, Anna Maria; Teng, Min; Thomas, Christine; Varney, Michael David; Wallace, Michael Brennan
PATENT ASSIGNEE(S): Agouron Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 439 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001002369	A2	20010111	WO 2000-US18263	20000630

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,

LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW,
AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

BR 2000012352	A	20020514	BR 2000-12352	20000630
EP 1218348	A2	20020703	EP 2000-943375	20000630
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003503481	T2	20030128	JP 2001-507809	20000630
US 6531491	B1	20030311	US 2001-983786	20011025
US 6534524	B1	20030318	US 2001-983783	20011025
NO 2001005797	A	20020301	NO 2001-5797	20011128
BG 106380	A	20020930	BG 2002-106380	20020201

PRIORITY APPLN. INFO.: US 1999-142130P P 19990702
US 2000-609335 B3 20000630
WO 2000-US18263 W 20000630

OTHER SOURCE(S): MARPAT 134:100864

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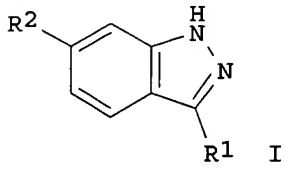

I

AB Indazole compds. I [R1 = substituted or unsubstituted aryl or heteroaryl, R3CH:CH, R3N:CH; R2 = substituted or unsubstituted aryl, heteroaryl, Y-X; R3 = substituted or unsubstituted alkyl alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl; Y = O, S, C(:CH2), CO, SO, SO2, alkylidene, NH, N(C1-C8 alkyl); X = substituted or unsubstituted aryl, heteroaryl, NH(alkyl), NH(cycloalkyl), NH(heterocycloalkyl), NH(aryl), NH(heteroaryl), NH(alkoxy), NH(dialkylamide)] and their pharmaceutically acceptable **prodrugs**, active metabolites, and salts are disclosed. The compds. modulate and/or inhibit the activity of certain protein kinases. In particular, I and pharmaceutical compns. contg. them are capable of mediating tyrosine kinase signal transduction, and thereby modulate and/or inhibit unwanted cell proliferation. The invention is also directed to the therapeutic or prophylactic use of pharmaceutical compns. contg. such compds., and to methods of treating cancer and other disease states assocd. with unwanted angiogenesis and/or cellular proliferation, such as diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis, and psoriasis, by administering effective amts. of such compds. E.g., I [R1 = (E)-3,4-(MeO)2C6H3CH:CH; R2 = 4-HO-3-MeOC6H3] (II) was prepd. from 6-aminoindazole by diazotization and substitution with iodide, protection of the indazole nitrogen with 2,4,6-Me3C6H2SO2Cl, coupling of the regioisomeric mixt. with 4-(methoxymethoxy)-3-methoxybenzeneboronic acid in the presence of dichlorobis(triphenylphosphine)palladium, and deprotection of the indazole moiety and iodination at the 3-position of the indazole. Treatment of the 3-indazolyl iodide with sec-butyllithium, phenyllithium, and DMF, regioselective protection of the indazole with 2,4,6-Me3C6H2SO2Cl, olefination with 3,4-dimethoxybenzyltriphenylphosphonium bromide, deprotection of the indazole, deprotection of the methoxymethyl group, and equilibration of the double bond with iodine gave II. Biol. data on protein kinase inhibition, cell proliferation inhibition, neovascularization inhibition, and i.p. and oral bioavailability, are given.

L41 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:384179 CAPLUS
DOCUMENT NUMBER: 133:30741
TITLE: Substituted piperazinone derivatives and other oxoazaheterocyclyl compounds useful as factor Xa inhibitors
INVENTOR(S): Ewing, William R.; Becker, Michael R.; Myers, Michael R.; Spada, Alfred P.
PATENT ASSIGNEE(S): Aventis Pharmaceuticals Products Inc., USA
SOURCE: PCT Int. Appl., 219 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000032590	A1	20000608	WO 1999-US28074	19991124
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 9937304	A1	19990729	WO 1999-US1682	19990127
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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PRIORITY APPLN. INFO.: US 1998-110012P A2 19981125
WO 1999-US1682 A2 19990127
US 1999-313611 A2 19990518
US 1999-363196 A2 19990728
US 1998-72707P A2 19980127
OTHER SOURCE(S): MARPAT 133:30741
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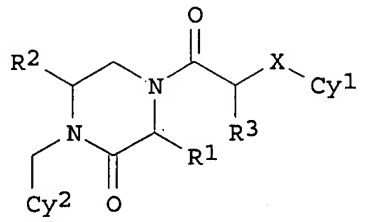

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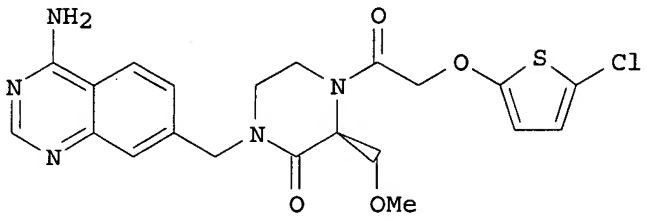


II

AB The invention is directed to piperazinones I and their pharmaceutically acceptable salts, **prodrugs**, N-oxides, hydrates, and solvates [wherein R1 = H, alkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, alkoxy, aminoalkyl, CH2OZ, CH(CH3)OZ; R2 = H, (un)substituted alkyl, aryl, aralkyl, heteroaryl, or heteroarylalkyl; R3 = H or Me; X = N or O; Z = lower alkyl or alkoxycarbonylalkyl; Cy1 = (un)substituted aryl, (un)substituted heteroaryl; Cy2 = (un)substituted aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl, etc.]. The compds. inhibit factor Xa (no data), and thereby the prodn. of thrombin, and are thus useful as anticoagulants in the treatment of a wide variety of conditions. The invention is also directed to pharmaceutical compns., synthetic intermediates, and a method of inhibiting factor Xa. Examples include the synthesis of approx. 780 invention compds., approx. 50 of which are also claimed, and several hundred intermediates. For instance, condensation of 5-chloro-2-thienyloxyacetic acid with the corresponding N-benzyloxycarbonyl-protected piperazinone deriv. (prepns. given), using DIPEA and TBTU in DMF, gave the preferred title compd. II.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:141730 CAPLUS

DOCUMENT NUMBER: 132:334367

TITLE: Synthesis and antitumor activity of duocarmycin derivatives: modification at C-8 position of A-ring pyrrole compounds bearing the simplified DNA-binding groups

AUTHOR(S): Amishiro, N.; Nagamura, S.; Murakata, C.; Okamoto, A.; Kobayashi, E.; Asada, M.; Gomi, K.; Tamaoki, T.; Okabe, M.; Yamaguchi, N.; Yamaguchi, K.; Saito, H.

CORPORATE SOURCE: Pharmaceutical Research Institute, Kyowa Hakko Kogyo Company, Ltd., Nagaizumi, Sunto, Shizuoka, Japan

SOURCE: Bioorganic & Medicinal Chemistry (2000), 8(2), 381-391
CODEN: BMECEP; ISSN: 0968-0896

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 132:334367

AB A series of the 8-O-substituted A-ring pyrrole derivs. of duocarmycin bearing the simplified DNA-binding moieties such as **cinnamoyl** or heteroaryl-acryloyl groups were synthesized, and evaluated for in vitro anticellular activity against HeLa S3 cells and in vivo antitumor activity

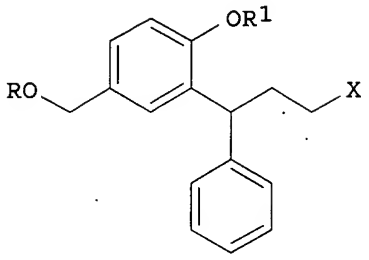
against murine sarcoma 180 in mice. In addn., the stability of the 8-O-substituted analogs in aq. soln. and the conversion to their active form (cyclopropane compd.) from the 8-O-substituted analogs in mice or human serum were examd. The 8-O-substituted A-ring pyrrole derivs. bearing the simplified DNA-binding moieties showed remarkably potent in vivo antitumor activity and low peripheral blood toxicity compared with the 8-O-substituted A-ring pyrrole derivs. having the trimethoxyindole skeleton in segment-B (Seg-B), which were equal to 8-O-[(N-methylpiperazinyl)carbonyl] derivs. of 4'-methoxycinnamates and 4'-methoxy-.beta.-heteroarylacrylates. Moreover, among 8-O-substituted analogs, several compds. can be chem. or enzymically converted to their active form in human serum. This result indicated that new 8-O-substituted derivs. were different **prodrugs** from KW-2189 and 8-O-substituted analogs being the same type of prodrug as KW-2189.

L41 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:736261 CAPLUS
DOCUMENT NUMBER: 131:336818
TITLE: Preparation of 3,3-diphenylpropylamines as antimuscarinic agents.
INVENTOR(S): Sparf, Bengt; Meese, Claus O.
PATENT ASSIGNEE(S): Schwarz Pharma AG, Germany
SOURCE: Eur. Pat. Appl., 27 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 957073	A1	19991117	EP 1998-108608	19980512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2328920	AA	19991118	CA 1999-2328920	19990511
WO 9958478	A1	19991118	WO 1999-EP3212	19990511
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9941412	A1	19991129	AU 1999-41412	19990511
AU 748057	B2	20020530		
BR 9910406	A	20010109	BR 1999-10406	19990511
EP 1077912	A1	20010228	EP 1999-924929	19990511
EP 1077912	B1	20020703		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AT 220056	E	20020715	AT 1999-924929	19990511
EP 1254890	A1	20021106	EP 2002-13481	19990511
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
NZ 507487	A	20021126	NZ 1999-507487	19990511
ES 2181443	T3	20030216	ES 1999-924929	19990511
RU 2199525	C2	20030227	RU 2000-125813	19990511
JP 2003519079	T2	20030617	JP 2000-548284	19990511
NO 2000005669	A	20010111	NO 2000-5669	20001110

PRIORITY APPLN. INFO.:
EP 1998-108608 A 19980512
EP 1999-924929 A3 19990511
WO 1999-EP3212 W 19990511

OTHER SOURCE(S): MARPAT 131:336818
GI



I

AB Title compds. (I; R = H, Me, Et, Pr, Me2CH, Bu, iso-Bu, pentyl, hexyl, PhCH2, alkyl, CHO, Ac, propionyl, isobutyryl, aminocarbonyl, aminosulfonyl, MeO2C, etc.; R1 = H, Me, Et, Pr, Me2CH, Bu, iso-Bu, pentyl, hexyl, PhCH2, alkyl, phenylalkyl; Z = NR8R9; R8, R9 = hydrocarbyl; NR8R9 = atoms to form a ring; with a proviso), were prepd. as antimuscarinic agents (no data). Thus, 4-bromophenol, **cinnamoyl** chloride, and Et3N were stirred 18 h in CH2Cl2 to give 99.8% 3-phenylacrylic acid 4-bromophenyl ester. This was refluxed 2 h with HOAc/H2SO4 to give 43.8% 6-bromo-4-phenylchroman-2-one. The latter was refluxed with benzyl bromide, K2CO3, and NaI in acetone/MeOH to give 102.1% crude Me 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionate, which was stirred with LiAlH4 in THF to give 96.3% 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol. This was stirred with tosyl chloride and pyridine in CH2Cl2 for 18 h to give 93.6% tosylate ester, which was refluxed 97 h with diisopropylamine in MeCN to give 77.9% [3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]diisopropylamine. The latter was converted in several steps to 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, which was acylated to give I.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:487215 CAPLUS
DOCUMENT NUMBER: 131:130007
TITLE: Substituted piperazinone derivatives and other oxoazaheterocyclyl compounds useful as factor Xa inhibitors
INVENTOR(S): Ewing, William R.; Becker, Michael R.; Choi-Sledeski, Yong Mi; Pauls, Heinz W.; He, Wei; Condon, Stephen M.; Davis, Roderick S.; Hanney, Barbara A.; Spada, Alfred P.; Burns, Christopher J.; Jiang, John Z.; Li, Aiwen; Myers, Michael R.; Lau, Wan F.; Poli, Gregory B.
PATENT ASSIGNEE(S): Rhone-Poulenc Rorer Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 300 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9937304	A1	19990729	WO 1999-US1682	19990127

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,

RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

ZA 9900607	A	19990727	ZA 1999-607	19990127	
CA 2319198	AA	19990729	CA 1999-2319198	19990127	
AU 9926533	A1	19990809	AU 1999-26533	19990127	
AU 745425	B2	20020321			
BR 9907300	A	20001024	BR 1999-7300	19990127	
EP 1051176	A1	20001115	EP 1999-906684	19990127	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2002501024	T2	20020115	JP 2000-528286	19990127	
EE 200000435	A	20020215	EE 2000-435	19990127	
WO 2000032590	A1	20000608	WO 1999-US28074	19991124	
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
NO 2000003808	A	20000926	NO 2000-3808	20000725	
BG 104633	A	20010330	BG 2000-104633	20000725	

PRIORITY APPLN. INFO.:

US 1998-72707P	A2	19980127
US 1998-110012P	A2	19981125
WO 1999-US1682	W	19990127
US 1999-313611	A2	19990518
US 1999-363196	A2	19990728

OTHER SOURCE(S): MARPAT 131:130007

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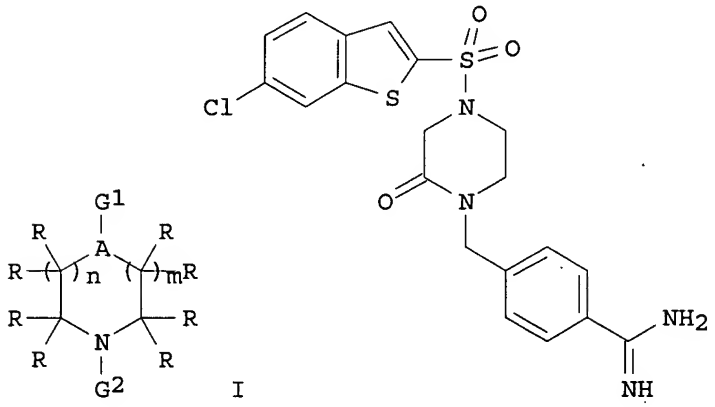

I II

AB The invention is directed to oxoazaheterocyclyl compds. I and their pharmaceutically acceptable salts, **prodrugs**, N-oxides, hydrates, and solvates [wherein A = CH, N; G1, G2 = (independently) -L-Cy; L = various at. and mol. linkers, including O, (un)substituted NH or S, alk(en/yn)ylene, etc., or their combinations; Cy = (un)substituted (hetero)aryl, cycloalk(en)yl, heterocyclyl, etc.; R = (independently) H, CO2H, alkoxycarbonyl, (un)substituted carbamoyl, alkyl, (hetero)aryl, (hetero)aralkyl; or two geminal R groups = O or S; m, n = 0-2; with provisos]. The compds. inhibit factor Xa (no data), and thereby the prodn. of thrombin, and are thus useful as anticoagulants in the treatment

of a wide variety of conditions. The invention is also directed to pharmaceutical compns., synthetic intermediates, and a method of inhibiting factor Xa. Examples include the synthesis of approx. 780 compds. I, which are also claimed, and several hundred intermediates. For instance, sulfonamidation of 6-chlorobenzo[b]thiophene-2-sulfonyl chloride with 4-(2-oxopiperazin-1-ylmethyl)benzamidine bistrifluoroacetate (prepns. given) in CH2Cl2 in the presence of Et3N gave title compd. II.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:136764 CAPLUS
DOCUMENT NUMBER: 130:196957
TITLE: Preparation of bicyclic peptide derivatives as interleukin-1.beta. converting enzyme inhibitors
INVENTOR(S): Batchelor, Mark James; Bebbington, David; Bemis, Guy W.; Fridman, Wolf Herman; Gillespie, Roger John; Golec, Julian M. C.; Lauffer, David J.; Livingston, David J.; Matharu, Saroop Singh; Mullican, Michael D.; Murcko, Mark A.; Murdoch, Robert; Zelle, Robert E.
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: U.S., 189 pp., Cont.-in-part of U.S. Ser. No. 575,641.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5874424	A	19990223	US 1996-598332	19960208
US 6008217	A	19991228	US 1995-575641	19951220
US 6204261	B1	20010320	US 1996-761483	19961206
IN 182290	A	19990306	IN 1996-CA2188	19961218
WO 9722619	A2	19970626	WO 1996-US20843	19961220
WO 9722619	A3	19971016		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9610798	A	19970707	ZA 1996-10798	19961220
AU 9715222	A1	19970714	AU 1997-15222	19961220
AU 735075	B2	20010628		
EP 869967	A2	19981014	EP 1996-945318	19961220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9612258	A	19990713	BR 1996-12258	19961220
CN 1229412	A	19990922	CN 1996-199828	19961220
NZ 326610	A	20000825	NZ 1996-326610	19961220
JP 2002507961	T2	20020312	JP 1997-523098	19961220
JP 2003137896	A2	20030514	JP 2002-306094	19961220
NO 9802597	A	19980812	NO 1998-2597	19980605
US 6258948	B1	20010710	US 1999-400639	19990921
US 6423840	B1	20020723	US 2001-773477	20010131
AU 756253	B2	20030109	AU 2001-76122	20010928

PRIORITY APPLN. INFO.:
US 1995-575641 A2 19951220
US 1996-598332 A2 19960208
US 1996-712878 A2 19960912
US 1996-31495P P 19961126
US 1996-761483 A 19961206

AU 1997-15222 A3 19961220
JP 1997-523098 A3 19961220
WO 1996-US20843 W 19961220

OTHER SOURCE(S): MARPAT 130:196957

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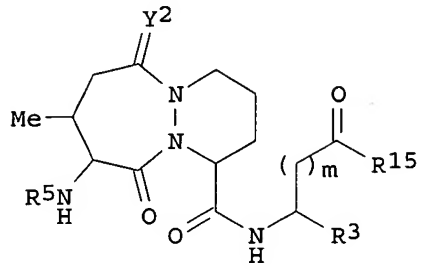

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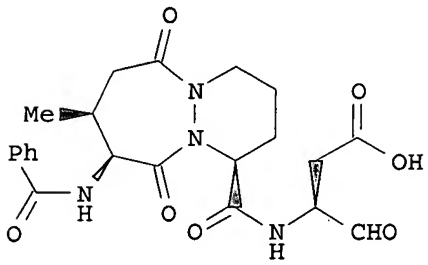


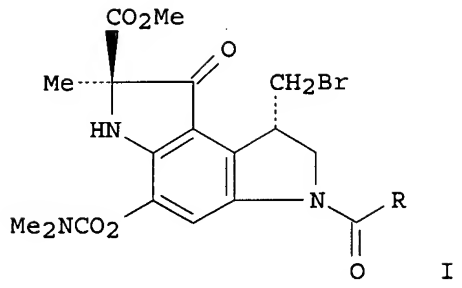
II

AB Title compds. I [m = 1-2; R3 = CN, CHO, COCH2-T1-R11, COCH2F, C:NOR9, COAr2; R5 = COR10, CO2R9, CONR102, SO2R9, SO2NHR10, COCH2OR9, COCOR10, R9, H, COCO2R10, COCONR9R10; Y = O, H2; T1 = O, S, S(O), SO2; R9 = Ar3, (un)branched C1-6 alkyl optionally unsatd. and optionally substituted with Ar3; R10 = H, Ar3, C3-6 cycloalkyl, any group R9; R11 = Ar4, (CH2)1-3Ar4, H, COAr4; R15 = OH, OAr3, NHOH, (un)branched C1-6 alkoxy optionally unsatd. and optionally substituted with Ar3, CONH2, OR5, OH, OR9, CO2H; Ar2 = (un)substituted 2-oxazolyl, 2-benzoxazolyl, 2-thiazolyl, 2-benzothiazolyl; Ar3, Ar4 = optionally substituted, nitrogen-contg. heteroarom. or heterocyclic group contg. 1-3 rings] were prepd. as inhibitors of interleukin-1.beta. converting enzyme. Thus, bicyclic peptide deriv. II was prepd. and shown to have Ki = 13 nM in a UV-visible assay and IC50 = 11000 nM in a peripheral blood mononuclear cell (PBMC) assay.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L41 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1996:368752 CAPLUS
DOCUMENT NUMBER: 125:114354
TITLE: Synthesis and antitumor activity of novel duocarmycin derivatives
AUTHOR(S): Asai, Akira; Nagamura, Satoru; Kobayashi, Eiji; Gomi, Katushige; Saito, Hiromitsu
CORPORATE SOURCE: Tokyo Res. Lab., Kyowa Hakko Kogyo Co. Ltd., Tokyo, 194, Japan
SOURCE: Bioorganic & Medicinal Chemistry Letters (1996), 6(11), 1215-1220
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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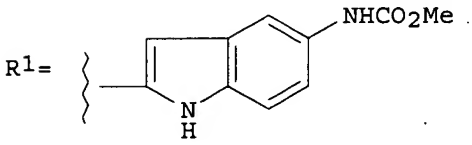

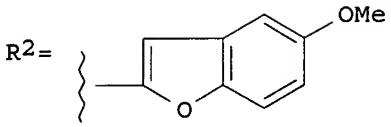

AB A series of Duocarmycin B2 analogs I [R = R1, R2, (E)-CH:CHC6H4OMe-4, (E)-CH:CHC6H4(NHMe)-4, CH2OC6H4OMe-4] bearing simplified right hand segments (Seg-Bs) with the protected phenolic hydroxyl group in left hand segment (Seg-A) was synthesized. Among them, the **cinnamoyl** derivs. I [R = (E)-CH:CHC6H4OMe-4, (E)-CH:CHC6H4(NHMe)-4] exhibited potent antitumor activity against in vivo murine tumor models in the wider range of doses without detectable toxic effects than DUMB2.

L41 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:298470 CAPLUS
DOCUMENT NUMBER: 120:298470
TITLE: **Prodrugs** of antiinflammatory 3-acyl-2-oxindole-1-carboxamides
INVENTOR(S): Barth, Wayne E.; Cooper, Kelvin; Kleinman, Edward F.; Reiter, Lawrence A.; Robinson, Ralph P.
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: U.S., 24 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5270331	A	19931214	US 1993-9188	19930126
CA 2152919	AA	19940804	CA 1993-2152919	19931020
CA 2152919	C	19990105		
WO 9417061	A1	19940804	WO 1993-US9813	19931020
W: AU, BR, CA, CZ, JP, KR, NO, NZ, PL, RU, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9453598	A1	19940815	AU 1994-53598	19931020
AU 678187	B2	19970522		
EP 681580	A1	19951115	EP 1993-923879	19931020
EP 681580	B1	19970709		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
BR 9307768	A	19951121	BR 1993-7768	19931020
JP 08501316	T2	19960213	JP 1993-511478	19931020
JP 2703825	B2	19980126		
CZ 281046	B6	19960612	CZ 1995-1819	19931020

AT 155137	E	19970715	AT 1993-923879	19931020
ES 2104187	T3	19971001	ES 1993-923879	19931020
RU 2124514	C1	19990110	RU 1995-117091	19931020
PL 178857	B1	20000630	PL 1993-309989	19931020
SK 280929	B6	20000912	SK 1995-912	19931020
IL 108384	A1	19981227	IL 1994-108384	19940120
HR 940034	B1	20001031	HR 1994-940034	19940121
ZA 9400463	A	19950724	ZA 1994-463	19940124
FI 9400365	A	19940727	FI 1994-365	19940125
CN 1097740	A	19950125	CN 1994-100697	19940125
CN 1052003	B	20000503		
HU 69689	A2	19950928	HU 1994-209	19940125
NO 9502949	A	19950725	NO 1995-2949	19950725

PRIORITY APPLN. INFO.: US 1993-9188 A 19930126
WO 1993-US9813 W 19931020

OTHER SOURCE(S): MARPAT 120:298470

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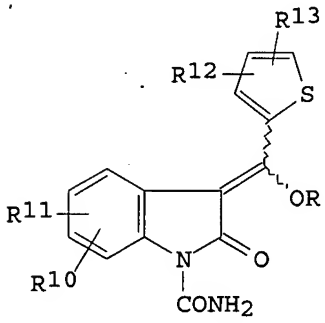

I

AB The title compds. [I; R = (un)substituted carbonyl-contg. chain, etc.; R10-R13 = H, C1-4 alkyl, halogen], which are antiinflammatory and analgesic **prodrugs** (no data), are prepd. Thus, 3-[hydroxy-2-(thienyl)methylene]-6-chloro-5-fluoro-2,3-dihydro-2-oxo-1H-indole-1-carboxamide was condensed with 4-MeOC6H4COCl, producing 6-chloro-5-fluoro-2,3-dihydro-3-[(4-methoxybenzoyl)oxy(2-thienyl)methylene]-2-oxo-1-H-indole-1-carboxamide, m.p. 220-221.degree..

L41 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER:	1994:270180 CAPLUS
DOCUMENT NUMBER:	120:270180
TITLE:	Free radical scavenger **prodrugs** - potentially potent brain penetrating agents
AUTHOR(S):	Benes, L.; Pronayova, Nad'a
CORPORATE SOURCE:	Fac. Pharm., Comenius Univ., Bratislava, Slovakia
SOURCE:	Pharmazie (1994), 49(1), 69-70 CODEN: PHARAT; ISSN: 0031-7144
DOCUMENT TYPE:	Journal
LANGUAGE:	English

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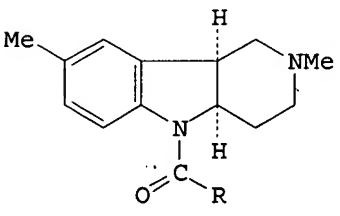


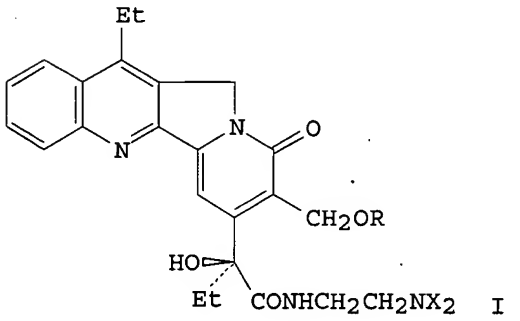
I

AB The title compds. [I, R = Me, (CH2)nMe, n = 5, 7, 8, 10, 12, 14, styryl] were prepd. by acylation of stobadine with RCOCl. The lipophilicity of I increased with the prolongation of the alkyl chain.

L41 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1989:231607 CAPLUS
DOCUMENT NUMBER: 110:231607
TITLE: Preparation of 7-ethylcamptothecin (aminoethyl)amide derivatives as antitumor **prodrugs**
INVENTOR(S): Sawada, Seigo; Nokata, Kenichiro; Okajima, Satoru; Nagai, Hisako; Yaegashi, Takashi; Tezuka, Kenichi; Miyasaka, Tadashi
PATENT ASSIGNEE(S): Yakult Honsha Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 30 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 296612	A1	19881228	EP 1988-110110	19880624
EP 296612	B1	19940622		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 1332413	A1	19941011	CA 1988-570315	19880623
JP 01131179	A2	19890524	JP 1988-154631	19880624
JP 2538792	B2	19961002		
US 4914205	A	19900403	US 1988-210918	19880624
ES 2058185	T3	19941101	ES 1988-110110	19880624

PRIORITY APPLN. INFO.: JP 1987-156495 19870625
OTHER SOURCE(S): MARPAT 110:231607
GI



I

AB The title compds. [I; X = lower alkyl; R = H, COY; Y = linear or branched, unsubstituted C1-18 alkyl, lower alkyl substituted by halo, NH2, acylamino, OH, lower alkoxy, aryloxy, or lower alkoxycarbonyl, C3-19 alkenyl or alkynyl, C3-8 cycloalkyl (substituted by acylamino-lower alkyl), N-acylpyrrolidyl, Ph (substituted by halo, CF3, NO2, NH2, lower alkoxycarbonyl, lower alkyl, Ph, or lower alkoxy), cinnamyl, PhCH2, naphthyl, pyridyl, furyl, thienyl], useful as antitumor agents (no data), were prepd. 7-Ethylcamptotecin (1.00 g) was stirred in 20 mL H2NCH2CH2NMe2 for 1 h at 50.degree. to give 70.7% I (R = H, X = Me).

L41 ANSWER 16 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2000185236 MEDLINE

DOCUMENT NUMBER: 20185236 PubMed ID: 10722161
TITLE: Synthesis and antitumor activity of duocarmycin derivatives: modification at C-8 position of A-ring pyrrole compounds bearing the simplified DNA-binding groups.
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AB A series of the 8-O-substituted A-ring pyrrole derivatives of duocarmycin bearing the simplified DNA-binding moieties such as **cinnamoyl** or heteroarylacryloyl groups were synthesized, and evaluated for in vitro anticellular activity against HeLa S3 cells and in vivo antitumor activity against murine sarcoma 180 in mice. In addition, the stability of the 8-O-substituted analogues in aqueous solution and the conversion to their active form (cyclopropane compound) from the 8-O-substituted analogues in mice or human serum were examined. The 8-O-substituted A-ring pyrrole derivatives bearing the simplified DNA-binding moieties showed remarkably potent in vivo antitumor activity and low peripheral blood toxicity compared with the 8-O-substituted A-ring pyrrole derivatives having the trimethoxyindole skeleton in segment-B (Seg-B), which were equal to 8-O-[(N-methylpiperazinyl)carbonyl] derivatives of 4'-methoxycinnamates and 4'-methoxy-beta-heteroarylacrylates. Moreover, among 8-O-substituted analogues, several compounds can be chemically or enzymatically converted to their active form in human serum. This result indicated that new 8-O-substituted derivatives were different **prodrugs** from KW-2189 and 8-O-substituted analogues being the same type of prodrug as KW-2189.

(150-175 mg kg-1, i.v.). In contrast, death induced by i.v. collagen (1.25 mg kg-1) plus adrenaline (75 .mu.g kg-1) is not significantly affected by defibrotide pretreatment. The inhibitory effect of defibrotide in mice is abolished following concomitant treatment with the inhibitor of fibrinolysis, tranexamic acid (100 mg kg-1, i.v.), but is unaffected following treatment with the cyclo-oxygenase inhibitor, aspirin (300 mg kg-1, i.p.). The protective effect of defibrotide against thrombin-induced thromboembolism in the mouse is potentiated by recombinant tissue-plasminogen activator (rt-PA; 1 mg kg-1, i.v.) or unfractionated heparin (10 u kg-1, i.v.) administration. The results suggest that defibrotide may possess antithrombotic activity on thrombin-induced thromboembolism which, at least in the mouse, may be partially mediated via induction of the fibrinolytic pathway.

L6 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1994:45613 CAPLUS
DOCUMENT NUMBER: 120:45613
TITLE: Effect of tribenoside on thrombin-induced decrease of rectal mucosal blood flow
AUTHOR(S): Iwata, Keiji; Yoshida, Masumi; Yamaguchi, Kazumasa; Kyuki, Kohei
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DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Improvement effect of tribenoside on dyscyclia was evaluated by measuring rectal mucosal blood flow in anesthetized rats with thrombin-induced decrease in rectal mucosal blood flow. Tribenoside was administered intrarectally, and rectal mucosal blood flow was measured using a laser flowmeter. In the nontreated groups, no changes in rectal mucosal blood flow were obsd. except for temporal slight increases immediately after administration of saline. In the dyscyclia-control group, marked decreases in rectal mucosal blood flow were obsd.; rectal mucosal blood flow of the dyscyclia-control group was markedly decreased immediately after **administration** of **thrombin**, showing lower values in comparison with the nontreated group throughout the observation period. In the tribenoside groups, marked suppression of decreases in rectal mucosal blood flow was obsd.; rectal mucosal blood flow of the tribenoside groups was decreased similarly to that of the dyscyclia-control group immediately after **administration** of **thrombin**, became almost the same as that of the dyscyclia-control group at 5 min after the **administration** of **thrombin** and increased from that time onward concn.-dependently. At 15 min (25%) or 20 min (10%) after the **administration** of **thrombin**, higher values of rectal mucosal blood flow were obtained in comparison with the dyscyclia-control group, and changes of rectal mucosal blood flow obsd. from that time onward were similar to those obsd. in the nontreated group. In the group treated with heparin Na, a pos. control, marked suppression of decreases in rectal mucosal blood flow was obsd.; rectal mucosal blood flow of the heparin Na group was almost the same as that before **administration** of **thrombin** throughout the observation period, showing higher values in comparison with the dyscyclia-control group, and changes of rectal mucosal blood flow were similar to those obsd. in the nontreated group. As described above, topical application of 10% and 25% solns. of tribenoside had a counteracting effect on dyscyclia in the rats with decrease in rectal mucosal blood flow induced by i.v. **administration** of **thrombin**. Tribenoside has a potential to alleviate hemorrhoids by improving rectal mucosal blood flow.

L6 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1992:424158 CAPLUS
DOCUMENT NUMBER: 117:24158

TITLE: The pharmacological modulation of thrombin-induced cerebral thromboembolism in the rabbit

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AB Intracarotid (i.c.) **administration** of **thrombin** induced a marked accumulation of 111indium-labeled platelets and 125I-labeled fibrinogen within the cranial vasculature of anesthetized rabbits. Thrombin (100 IU kg-1, i.c.)-induced platelet accumulation was completely abolished by pretreatment with desulfatohirudin (CGP 39393; 1 mg kg-1 i.c., 1 min prior to thrombin). Administration of CGP 39393 1 or 20 min after thrombin produced a redn. in platelet accumulation. I.v. administration of the platelet activating factor (PAF) receptor antagonist BN 52021 (10 mg kg-1) 5 min prior to thrombin (100 IU kg-1, i.c.) had no effect on platelet accumulation. An inhibitor of NO biosynthesis, L-NG-nitroarginine Me ester (L-NAME; 100 mg kg-1, i.c.), had no effect on the cranial platelet accumulation response to thrombin (10 IU kg-1, i.c.) when administered 5 min prior to thrombin. Defibrotide (32 or 64 mg kg-1 bolus i.c. followed by 32 or 64 mg kg-1 h-1, i.c., infusion for 45 min) treatment begun 20 min after thrombin (100 IU kg-1, i.c.) did not modify the cranial platelet accumulation response. Cranial platelet accumulation induced by thrombin (100 IU kg-1, i.c.) was reversed by the fibrinolytic drugs urokinase (20 IU kg-1, i.c., infusion for 45 min), anisoylated plasminogen streptokinase activator complex (APSAC) (200 mg kg-1, i.v. bolus) or recombinant tissue plasminogen activator (rt-PA; 100 .mu.g kg-1, i.c. bolus followed by 20 .mu.g kg-1 min-1, i.c., infusion for 45 min) administered 20 min after thrombin. APSAC had no effect when administered 3 h after thrombin. APSAC (200 .mu.g kg-1, i.v. bolus) reversed thrombin (100 IU kg-1, i.c.) - induced intracranial accumulation of 125I-fibrinogen when administered 20 min after thrombin. Apparently, neither endogenous PAF nor NO modulate thrombin-induced intracranial platelet accumulation in the rabbit. However, fibrin deposition appears to play an important role as shown by the ability of fibrinolytic agents to reverse platelet and fibrinogen accumulation induced by i.c. thrombin.